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Benchmark Dose Software (BMDS)
Version 2.1

User's Manual

Version 2.0

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1.0 GENERAL TOPICS

1.1 Overview

The U.S. Environmental Protection Agency (EPA) Benchmark Dose Software (BMDS) was developed as a tool to facilitate the application of benchmark dose (BMD) methods to EPA hazardous pollutant risk assessments. This help facility provides instruction on how to use the BMDS, but is not intended to address the EPA BMD methods. While the EPA BMD methods guidance has not been finalized at this time, every attempt has been made to make his software consistent with the most recent working draft guidance and discussions of the EPA Benchmark Dose Work group. The latest draft of the "Benchmark Dose Technical Guidance Document" (October, 2000) is undergoing an external, EPA Risk Assessment Fourm (RAF) review. Until formal BMD methods guidance is available, users of this software are strongly encouraged to review existing background material such as "The Use of the Benchmark Dose Approach in Health Risk Assessment" (EPA, 1995) before using this software.

Research into model development for BMDS started in 1995 and the first BMDS prototype was internally reviewed by EPA in 1997. After external and public reviews in 1998-1999, and extensive Quality Assurance testing in 1999-2000, BMDS version 1.2 was released in April, 2000. Subsequent versions were released up to version 1.4.1b in August 2007. This latest version of BMDS, version 2.1, replaces 1.4.1b and 2.0 and contains a wholly revamped user interface and new dichotomous models ("Dichotomous-Alternative" model type) as follows: Gamma-BgDose; Dichotomous Hill; Logistic-BgResponse; LogProbit-BgDose; Multistage-BgDose; Multistage-Cancer-BgDose; Probit-BgDose; Weibull-BgDose. Additional information about these new models is contained in the Help option "Alternative Models Help." Moreover, this version contains a new continuous model, Exponential, which consists of a set of four related models that can be run together or individually. A toxicodiffusion model has been added to model data sets where the response is measured at different times after exposure (a repeated measures model). Finally, a model called the "ten Berge" model has been added to analyze dichotomous responses where (at least) two independent variables are presumed to account for the response rates; this model has been used extensively for acute inhalation exposure experiments where the two explanatory variables are concentration and duration of exposure.

EPA uses BMD methods to estimate reference doses (RfDs) and reference concentrations (RfCs), which are used along with other scientific information to set standards for noncancer human health effects. Until recently, RfDs and RfCs have been determined from no-observed-adverse-effect levels (NOAELs), which represent the highest experimental dose for which no adverse health effects have been documented. Using the NOAEL in determining RfDs and RfCs has long been recognized as having limitations in that it 1) is limited to one of the doses in the study and is dependent on study design; 2) does not account for variability in the estimate of the dose-response; 3) does not account for the slope of the dose-response curve; and 4) cannot be applied when there is no NOAEL, except through the application of an uncertainty factor (Crump, 1984; Kimmel and Gaylor, 1988). A goal of the BMD approach is to define a starting point of departure (POD) for the computation of a reference value (RfD or RfC) or slope factor that is more independent of study design. The EPA Risk Assessment Forum has written guidelines for the use of the BMD approach in the assessment of noncancer health risk (U.S. EPA, 1995) and the EPA Benchmark Dose Workgroup is in the process of drafting technical guidance for the application of the BMD approach in cancer and noncancer dose-response assessments.

Use of BMD methods involve fitting mathematical models to dose-response data and using the different results to select a BMD that is associated with a predetermined benchmark response (BMR), such as a 10% increase in the incidence of a particular lesion or a 10% decrease in body weight gain. BMDS facilitates these operations by providing simple data-management tools and an easy-to-use interface to run multiple models on the same dose-response data set. Results from all models include a reiteration of the model formula and model run options chosen by the user, goodness-of-fit information, the BMD, and

the estimate of the lower-bound confidence limit on the BMD (BMDL). Model results are presented in textual and graphical output files which can be printed or saved and incorporated into other documents.

Running the models on a data set consists of five basic steps.

Step 1: Create a new session or open an existing session.

Step 2: Select the appropriate models based on the type of data set being evaluated.

Step 3: Create a data set using the BMDS spreadsheet capability or import a data file.

Step 4: Specify the parameters associated with the model selected by choosing or creating a new option file.

Step 5: Run the Model and view the tabular and graphical results.

More complete documentation for use of BMDS is provided within the remainder of this program's online help facility. Hard copy documentation is available from EPA's BMDS web site at http:/epa.gov/ncea/bmds.htm.

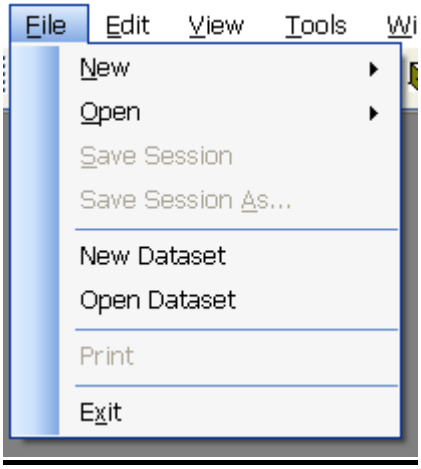
EPA plans to continually improve and expand the BMDS system. Use the BMDS web page at (http://epa.gov/ncea/bmds.htm) as your most up-to-date source of information and updates pertaining to the BMDS. The entire BMDS system or model updates can be downloaded from the web site. The source code files for the models used in the BMDS system are also available via the BMDS web site to reviewers and programmers who might be interested in performing an in-depth analysis of the model algorithms and features.

We welcome, in fact encourage, your comments on the BMDS software and the model source code files. Please provide comments, recommendations, suggested revisions, or corrections, to bmds.ncea@epa.gov.

1.2 Main Menu and Tool Bar

At all times throughout the running of the BMD software a menu bar and a tool bar appears at the top of the window. The following section will describe the different options provided by the menu bar. The Toolbar is the graphical representation of certain options under the "File" item on the menu bar. When applicable, the Toolbar icon associated with those "File" items are shown next to their description below.

File



New Creates a new Dose-Response session window.

Open Opens a previously saved session. Either a regular Dose-Response session (a file with the .ssn extension; see description below) or an existing ten Berge analysis (a file with the .ten extension) may be opened this way.

Save Session Saves the current session.

Save Session As... Saves the current session under a new file name.

New Dataset Create a new data set.

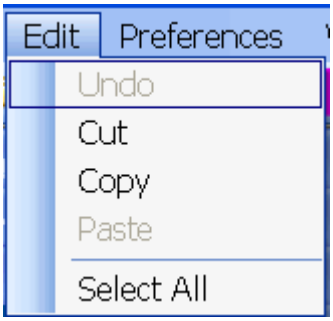
Open Dataset Opens an existing data file.

Print Prints the results of the current session.

Exit Exit the BMDS program.

Edit

The Edit menu commands assist with copying, cutting and pasting data within the BMDS output file. The commands can be implemented by selecting them from the menu with a mouse or by using the indicated key strokes.



Undo Paste (Ctrl+Z) Will undo a paste or cut.

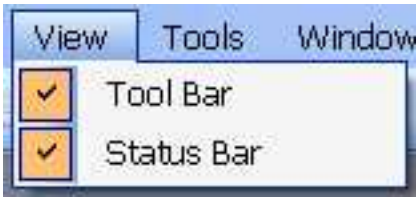
Cut (Ctrl+X) Selected data is cut from an active output file

Copy (Ctrl+C) Selected data is copied from an active output file; or a selected data file name is copied from the "Data File" column of an active session grid.

Paste (Ctrl+V) Cut/copied data is pasted into output file at cursor location.

Select All Selects all text in current active window.

View



Tool Bar Toggles the visibility of the tool bar and icons. A checkmark to the left of this option in the menu indicates the tool bar is visible.

Status Bar Toggles the visibility of the status bar at the bottom of the BDMS screen. A checkmark to the left of this option in the menu indicates the status bar is visible.

Tools

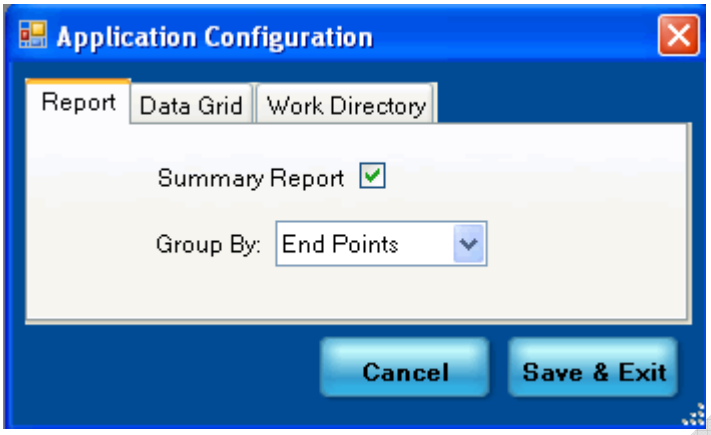
View Plot... Displays a plot file graph.

View Output File... Opens saved Output file in new window.

R Interface... Currently not implemented.

Options... Reveals option tabs for application configuration.

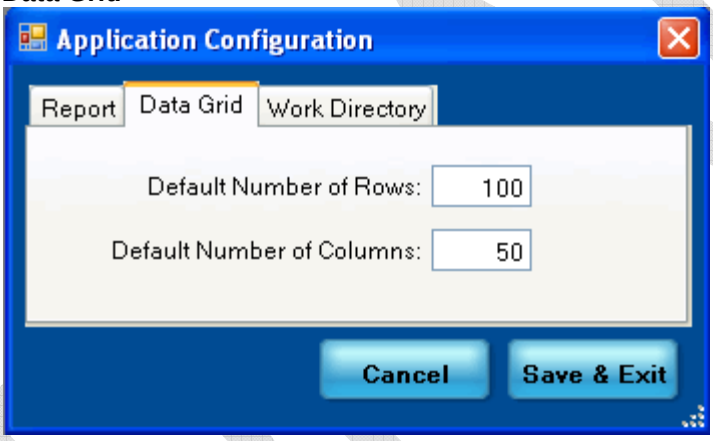
Report



Summary Report A checkmark to the right of this option indicates a summary report and summary plots will be displayed after a session "run." If left unchecked, the summary report is not generated and plots displayed in separate windows.

Group By This option determines how session "run" results (summary reports and summary plots) are grouped together. Results can be grouped by end points or by the data filename.

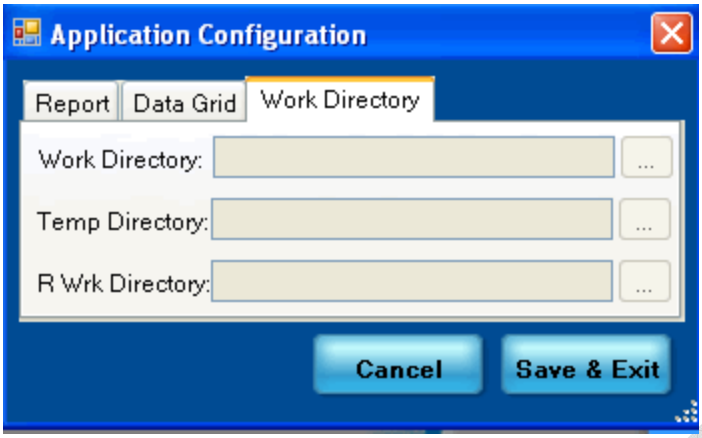
Data Grid



Default Number of Rows Determines how many rows appear when creating a new dataset.

Default Number of Columns Determines how many columns appear when creating a new dataset.

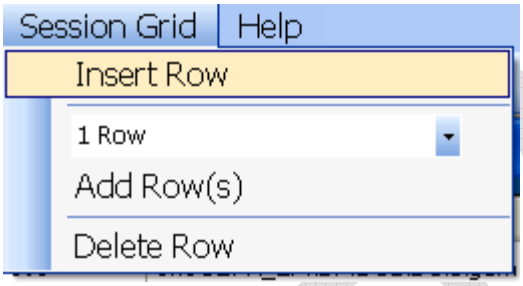
Working Directory



Options under this tab are currently not implemented.

Session Grid

This menu is available when a session window is open.



Insert Row Inserts a new row above the currently selected row in the session grid. The currently selected row is indicated by the black arrow to the left of the row number.

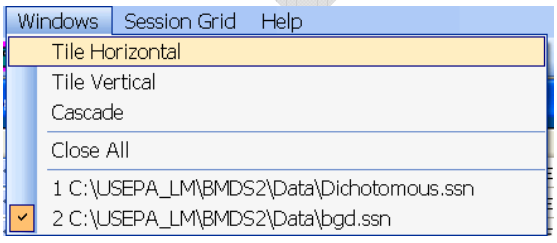
Drop down list Allows a predefined number of rows to be added to the session grid or all the models of a chosen group to be added.

Add Row(s) Used in conjunction with the drop down list described above. No action is taken until user selects from the list and clicks Add Row(s).

Delete Row Deletes the currently selected row in the session grid.

Windows

Options under the Windows menu are only available when multiple windows are open inside the BDMS program.



Tile Horizontal Tiles windows horizontally.

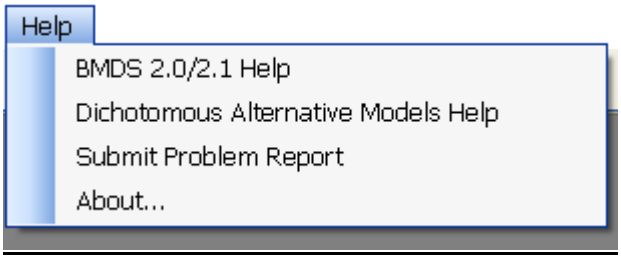
Tile Vertical Tiles windows vertically.

Cascade Displays windows in a cascade arrangement.

Close all Closes all windows inside the BDMS program.

Window List A list of currently open windows is displayed. Clicking on a particular window name will bring the selected window to the top. The current top window will have a checkmark to the left of its name.

Help



BMDS 2.0/2.1 Help Displays the contents of the Help documentation in a new window.

Dichotomous Alternative Models Help Information on the Alternative models is displayed in a new window.

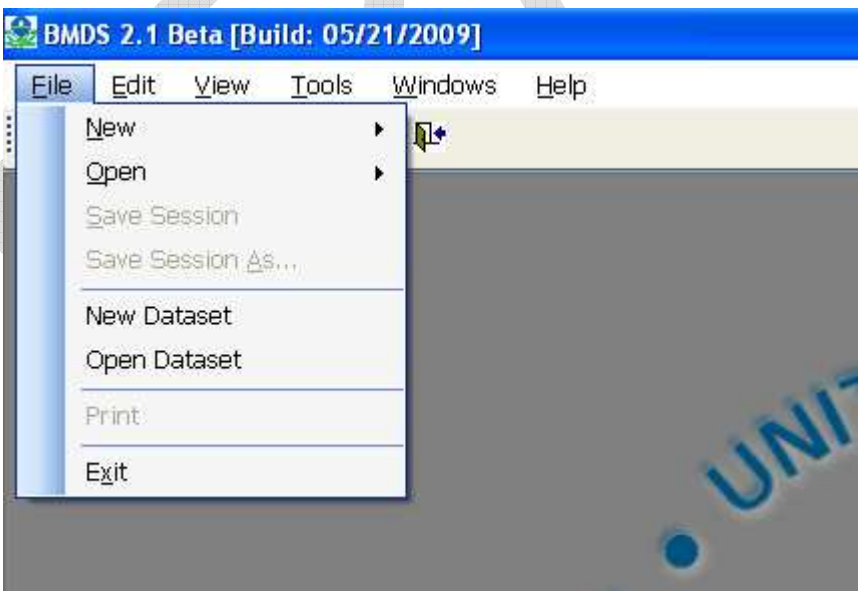
Submit Problem Report Currently not implemented.

About... Window describing the BMDS Sponsors and Credits, BMDS program version, and a disclaimer.

1.3 Running a Session

Step 1: Create a new session or open an existing session.

Use the menu or appropriate icons to create a new session or open an existing session.

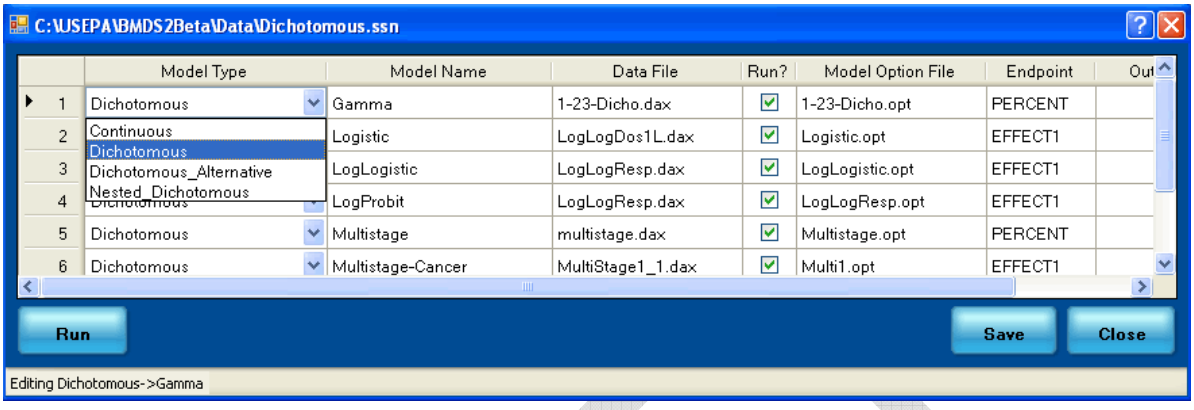


2

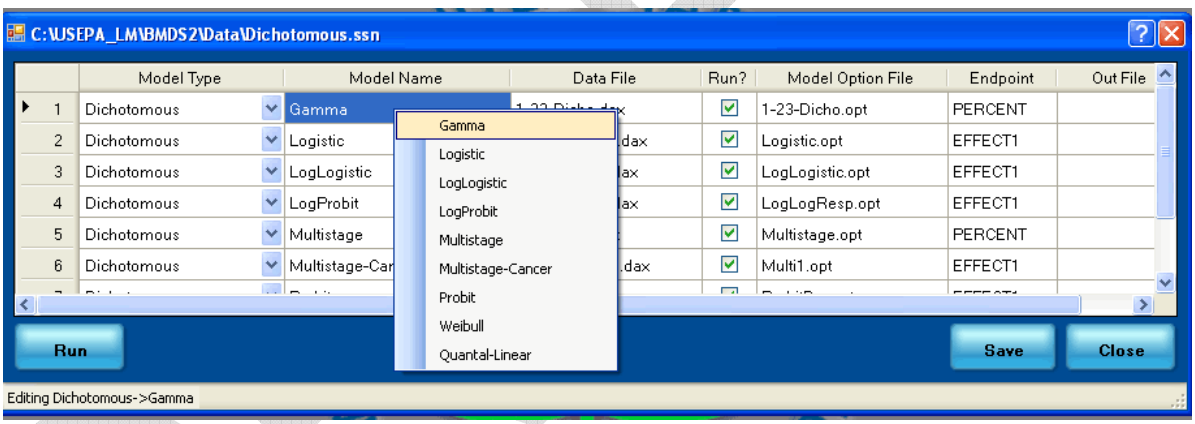
Step 2: Select the appropriate model(s) based on the type of data set being evaluated.

Once a session is open, a model type can be selected with the drop down box. BMDS is capable

of processing multiple sets of data and models. To add additional models to the session table, select Session Grid from the main menu. The Session Grid menu allows a single row or a user-determined number of rows to be added to the session table. There is also a Delete Row function.

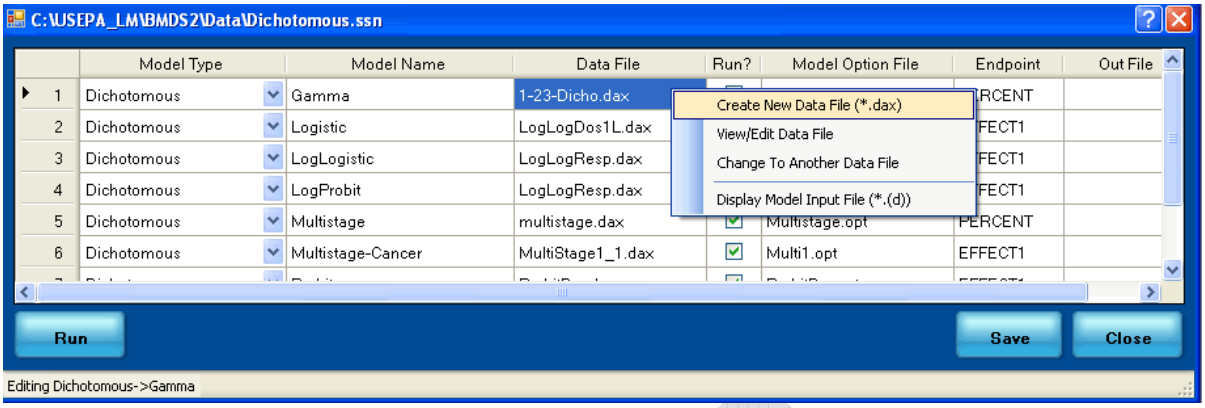


Right click on the row under the Model Name column. A menu will appear with a choice of models depending on the model group previously selected.

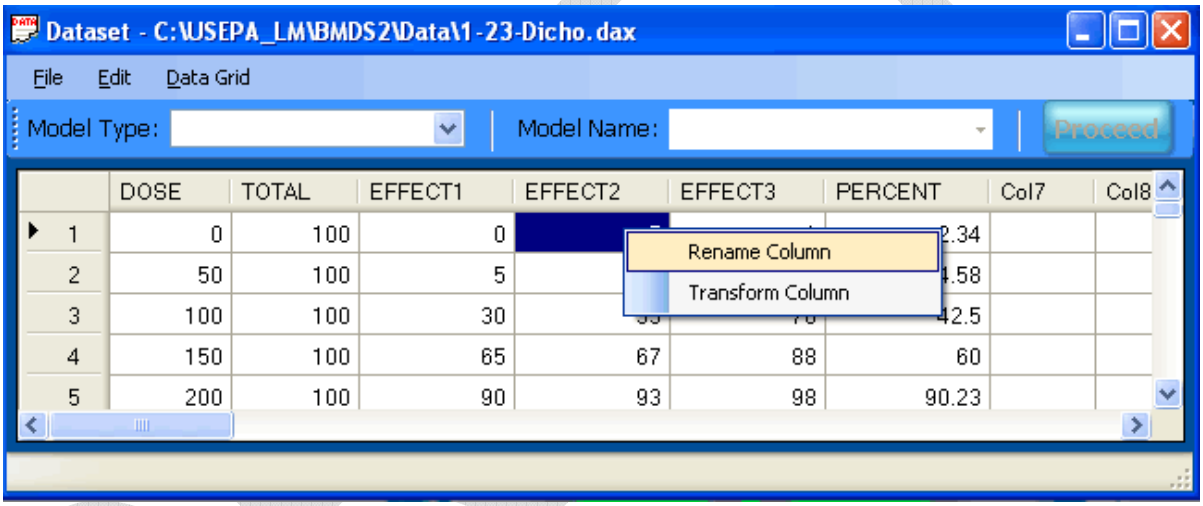


Step 3: Create a data set using the BMDS spreadsheet capability or import a data file.

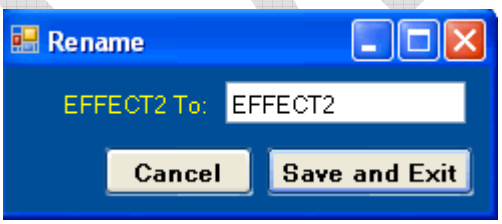
Data are stored in files with the .dax extension. A new data set can be created by right clicking on a field under the Data File column. Data may be created, edited or selected from an existing *.dax file.



The data entry and editing facility appears below. Right click in any column field (the column names) to display column options.



Select Rename to rename the column. Enter the new column name and use the Save and Exit button to make the change.



Select Transform Column to bring up the Variable Transformation window. Use this window to apply transformations on specified columns.

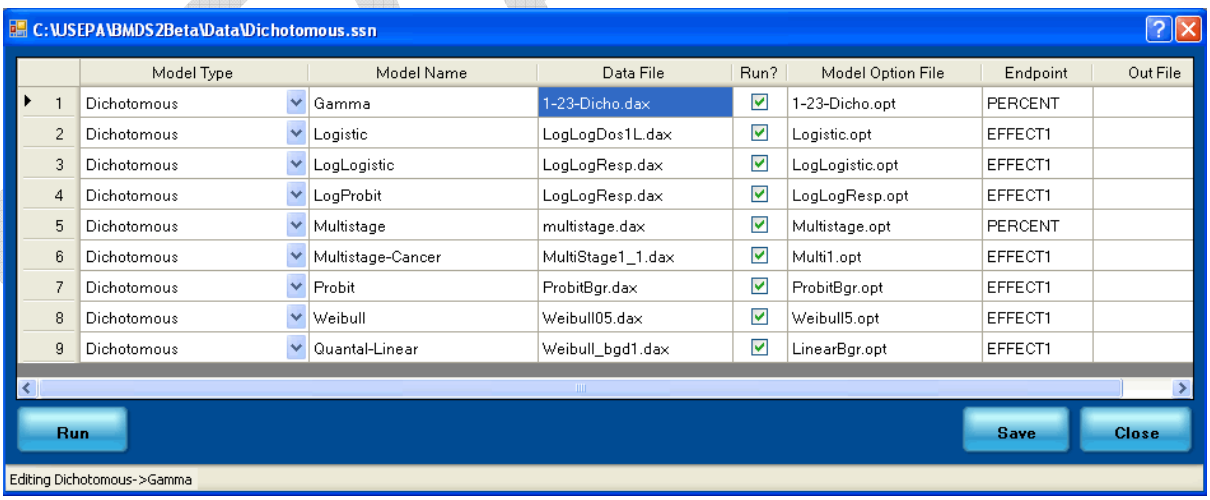
See sections 1.4, A, B, and C for additional manipulations of the data files. Once all the data are entered/modified as desired, the user may save and close the data grid screen. The appropriate data file name should be displayed in the session window under the Data File column.

Copy and Paste Feature

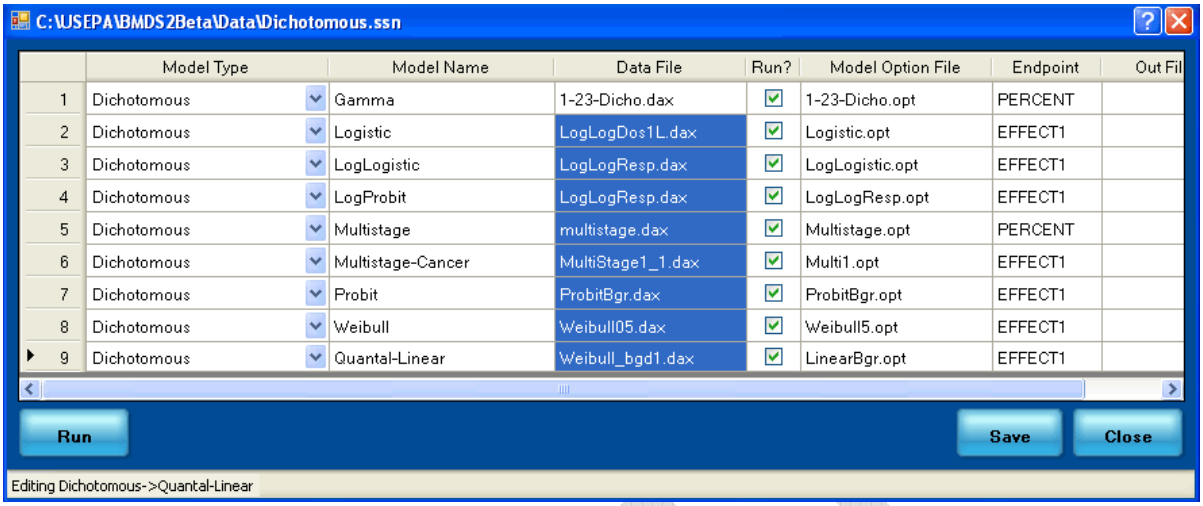
A copy and paste feature enables users to copy and paste the data file into multiple rows using CTRL-C to copy and CTRL-V to paste. Multiple rows can be copied or pasted at the same time. Rows are selected by holding a mouse click and dragging to highlight data. Alternatively, a SHIFT-CLICK method can be used vertically in either direction.

Example:

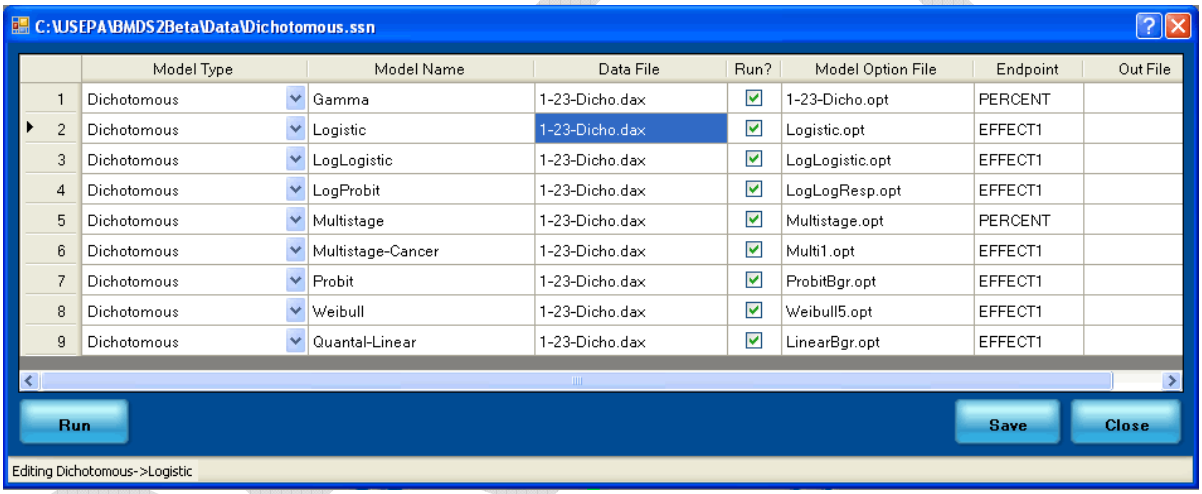
The copy and paste feature is useful for setting multiple models to use the same data file all at once instead of individually. In this example a data file is copied to multiple rows. CTRL-C is used to copy the data file highlighted.



Multiple rows under the Data File column are selected to receive the copied data file value.

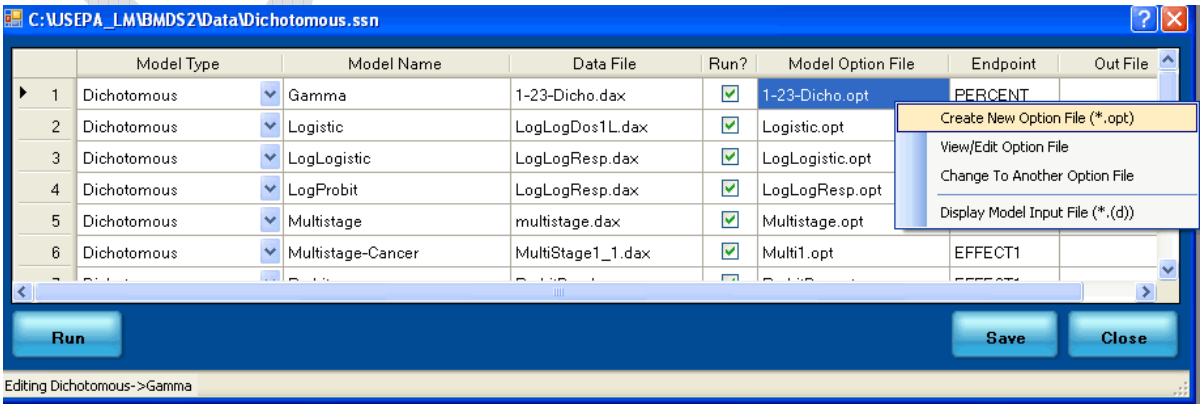


CTRL-V is used to paste the data file into multiple rows.

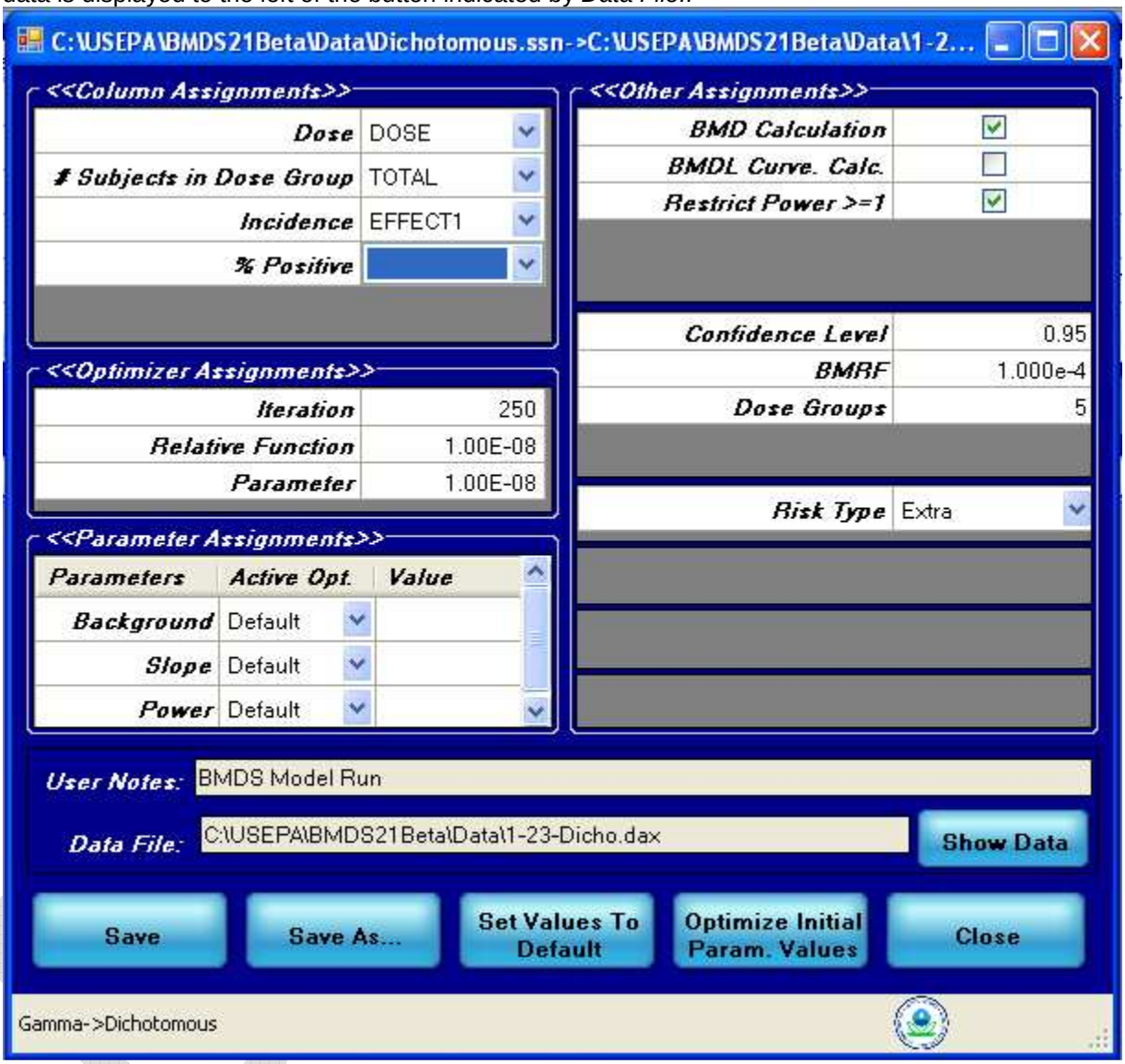


Step 4: Specify the parameters associated with the model selected by choosing or creating a new option file.

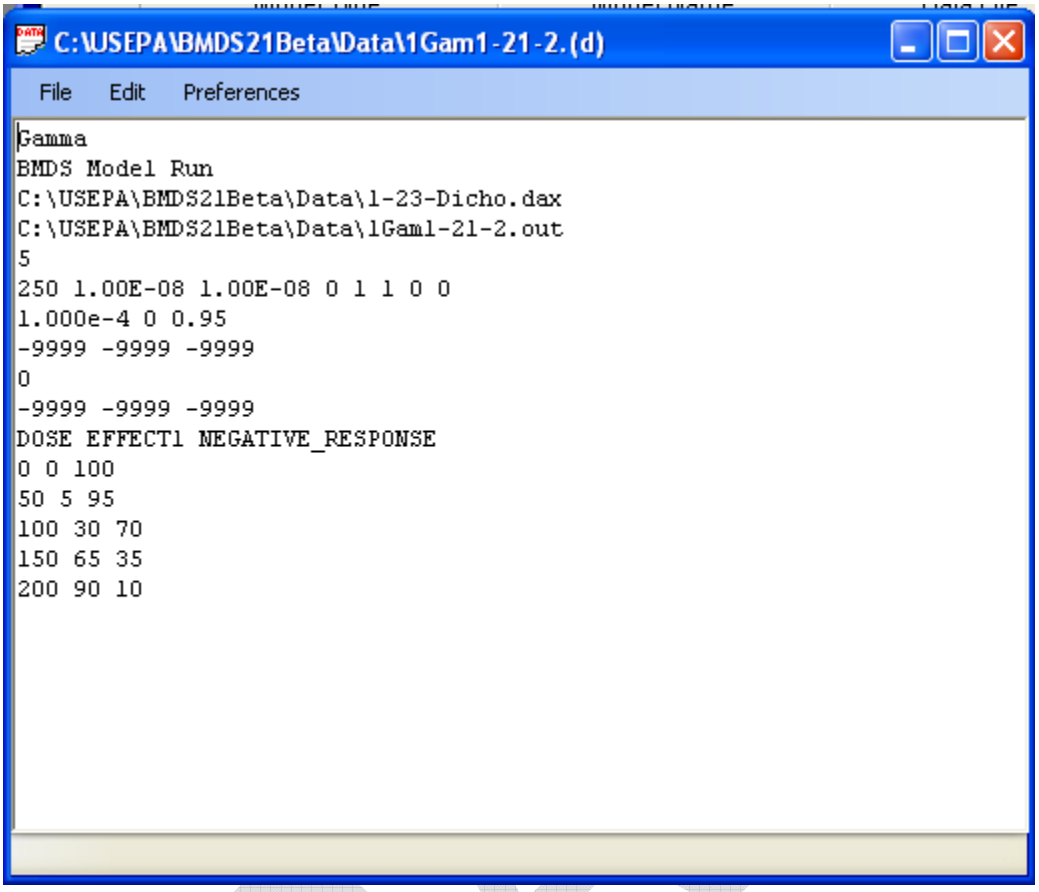
The option parameters are stored in files with the .opt extension. Right clicking on a field under the Model Option File column allows new option files to be created and existing option files to be selected or edited.



The display window below is used to view and edit the parameter options. Option files may be saved to a specified path, set to default values, and optimized using the buttons along the bottom of the window. The status bar displays which model and model type the parameters will affect. Data to be used in the model may also be seen by clicking the Show data button. The path to the data is displayed to the left of the button indicated by *Data File:*.

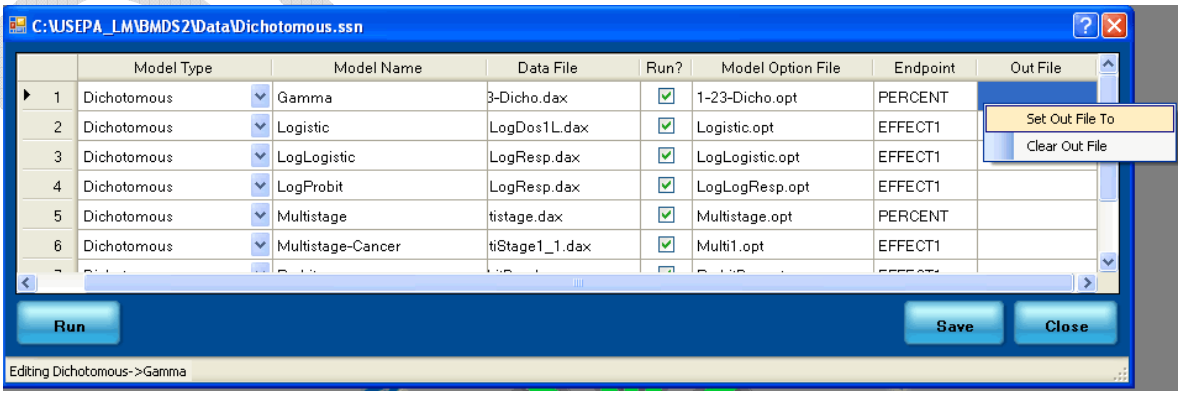


Select Display Model Input File (*.(d)) from the session screen to view the input file.

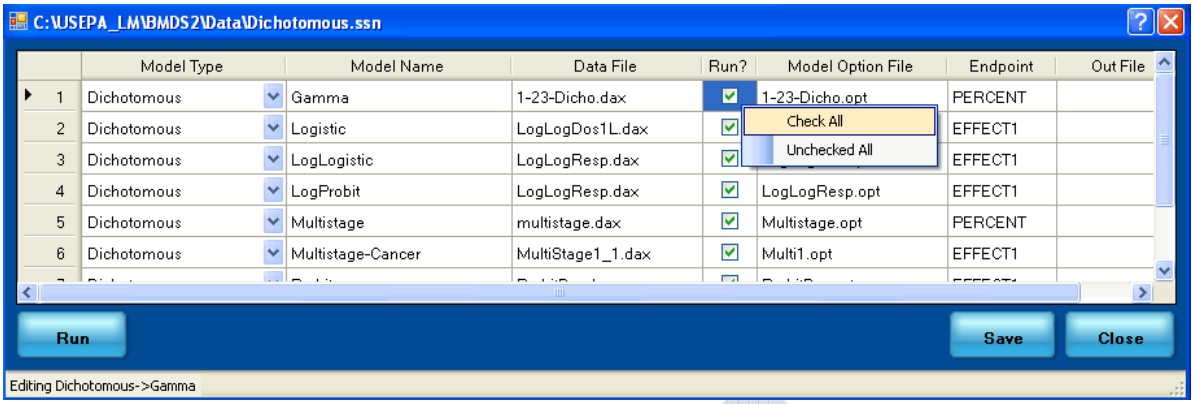


Step 5: Run the Model and view the textual and graphical results.

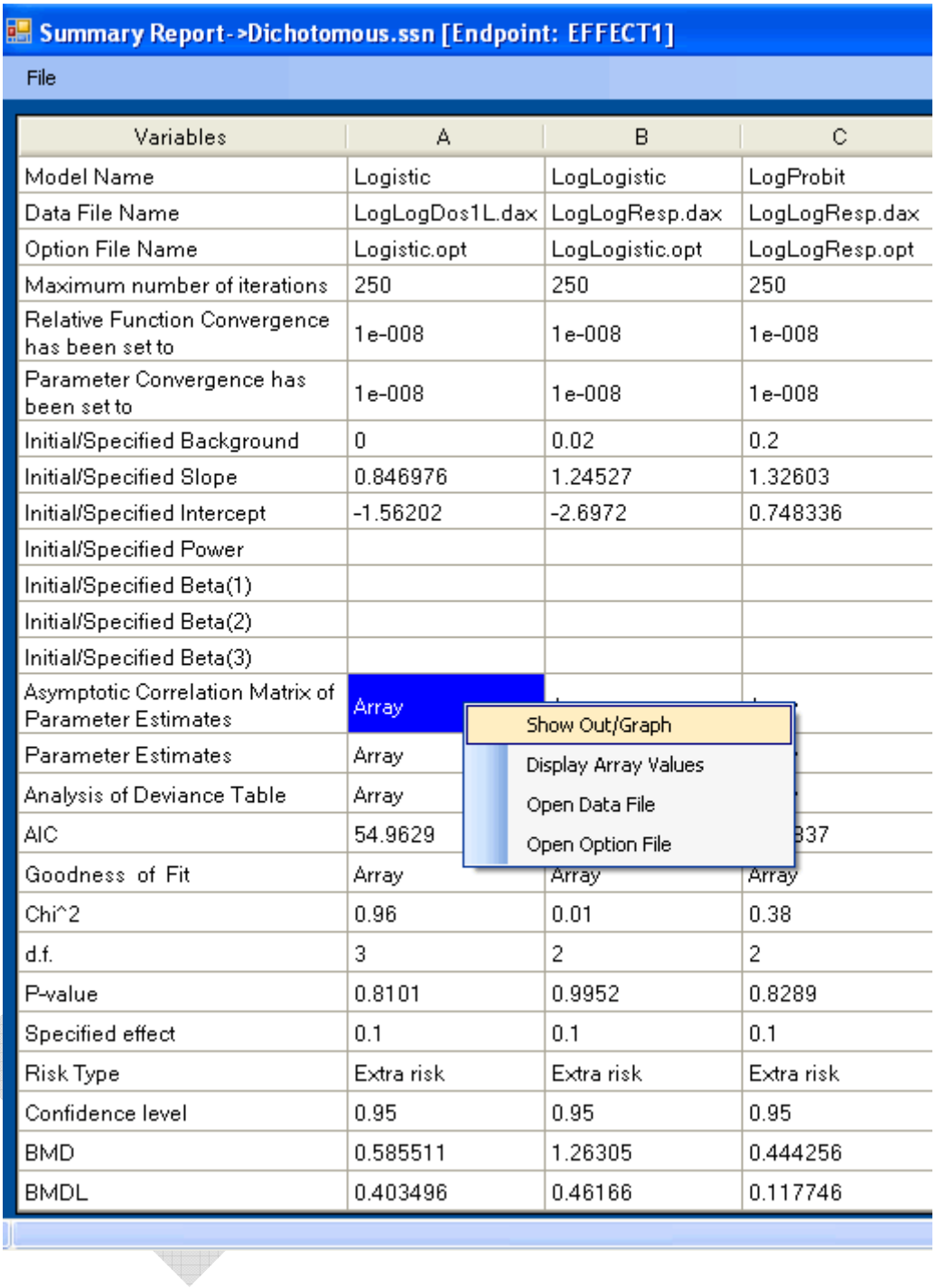
Right click in a specific cell in the Out File column to specify a file for saving output.



Select which models to be run by placing check marks in the appropriate rows under the Run? column. Right clicking will display a sub menu allowing all boxes to be checked or unchecked at once.

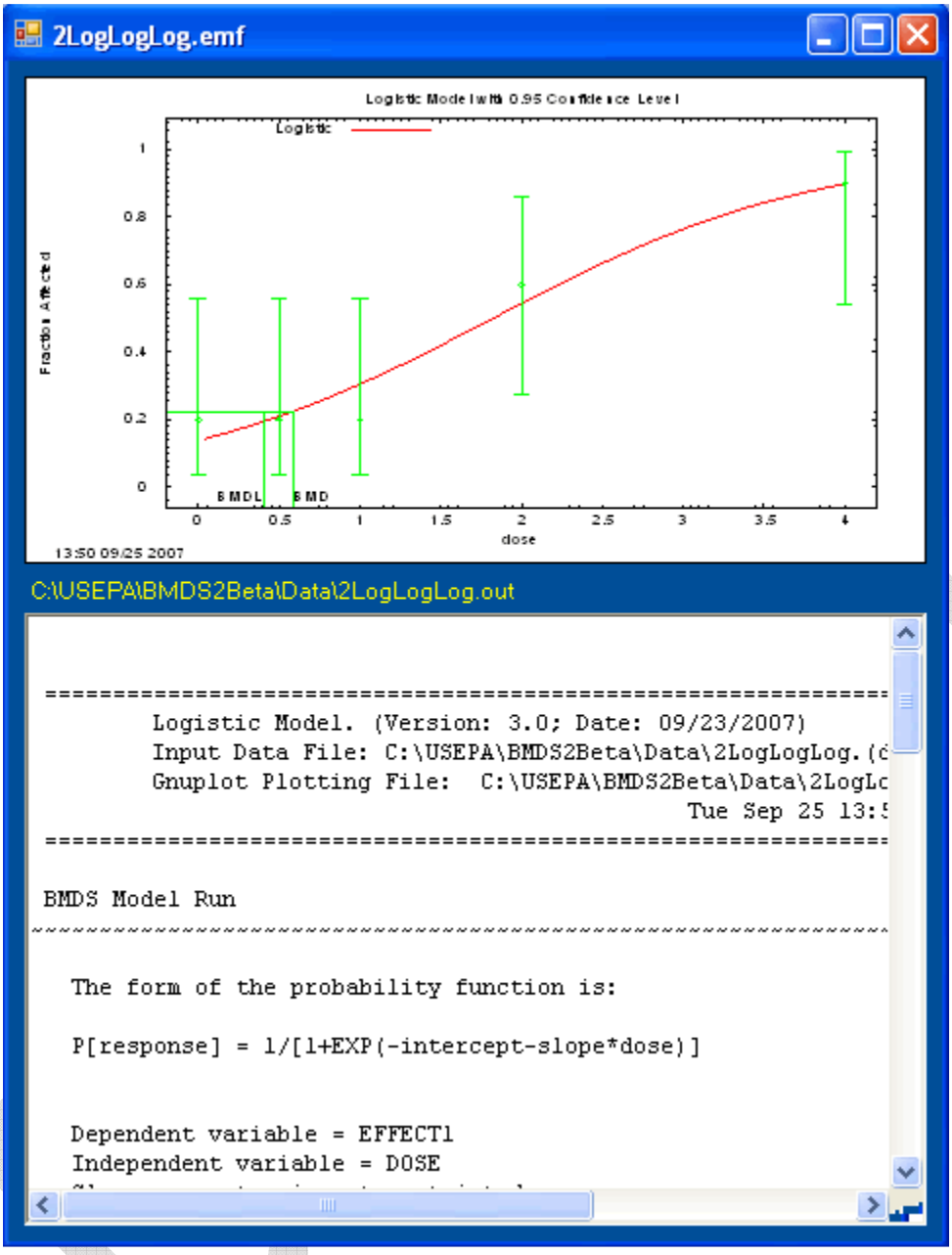


Click on the Run button on the bottom left of the session window. Two new windows will be opened, displaying a textual Summary Report and a Summary Graph of the results. The window below displays the variables set for each of the models run in a table format. Each lettered column corresponds to the models previously added in the session window. Right clicking in any lettered column will display a menu with options to Show Out/Graph, Display Array Values, Open Data File, or to Open Option File. To display array values, users must right click on a cell containing the word "Array."

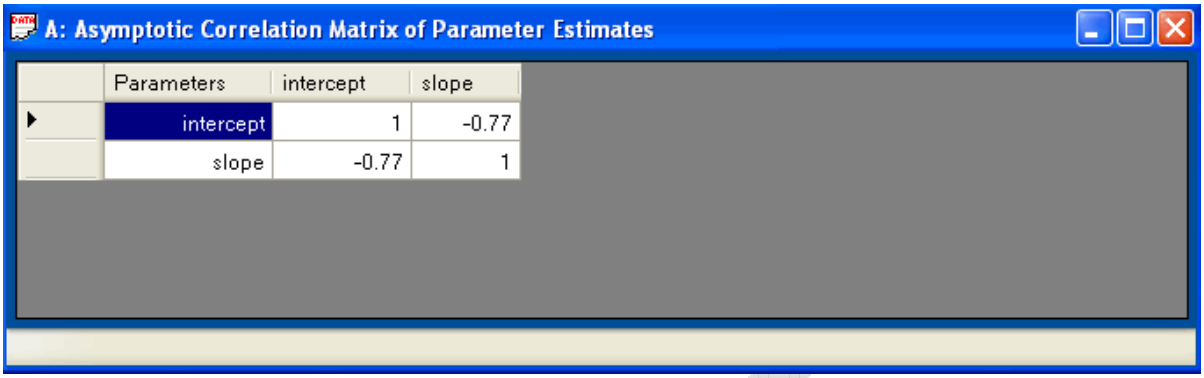


Variables	A	B	C
Model Name	Logistic	LogLogistic	LogProbit
Data File Name	LogLogDos1L.dax	LogLogResp.dax	LogLogResp.dax
Option File Name	Logistic.opt	LogLogistic.opt	LogLogResp.opt
Maximum number of iterations	250	250	250
Relative Function Convergence has been set to	1e-008	1e-008	1e-008
Parameter Convergence has been set to	1e-008	1e-008	1e-008
Initial/Specified Background	0	0.02	0.2
Initial/Specified Slope	0.846976	1.24527	1.32603
Initial/Specified Intercept	-1.56202	-2.6972	0.748336
Initial/Specified Power			
Initial/Specified Beta(1)			
Initial/Specified Beta(2)			
Initial/Specified Beta(3)			
Asymptotic Correlation Matrix of Parameter Estimates	Array		
Parameter Estimates	Array		
Analysis of Deviance Table	Array		
AIC	54.9629		337
Goodness of Fit	Array	Array	Array
Chi^2	0.96	0.01	0.38
d.f.	3	2	2
P-value	0.8101	0.9952	0.8289
Specified effect	0.1	0.1	0.1
Risk Type	Extra risk	Extra risk	Extra risk
Confidence level	0.95	0.95	0.95
BMD	0.585511	1.26305	0.444256
BMDL	0.403496	0.46166	0.117746

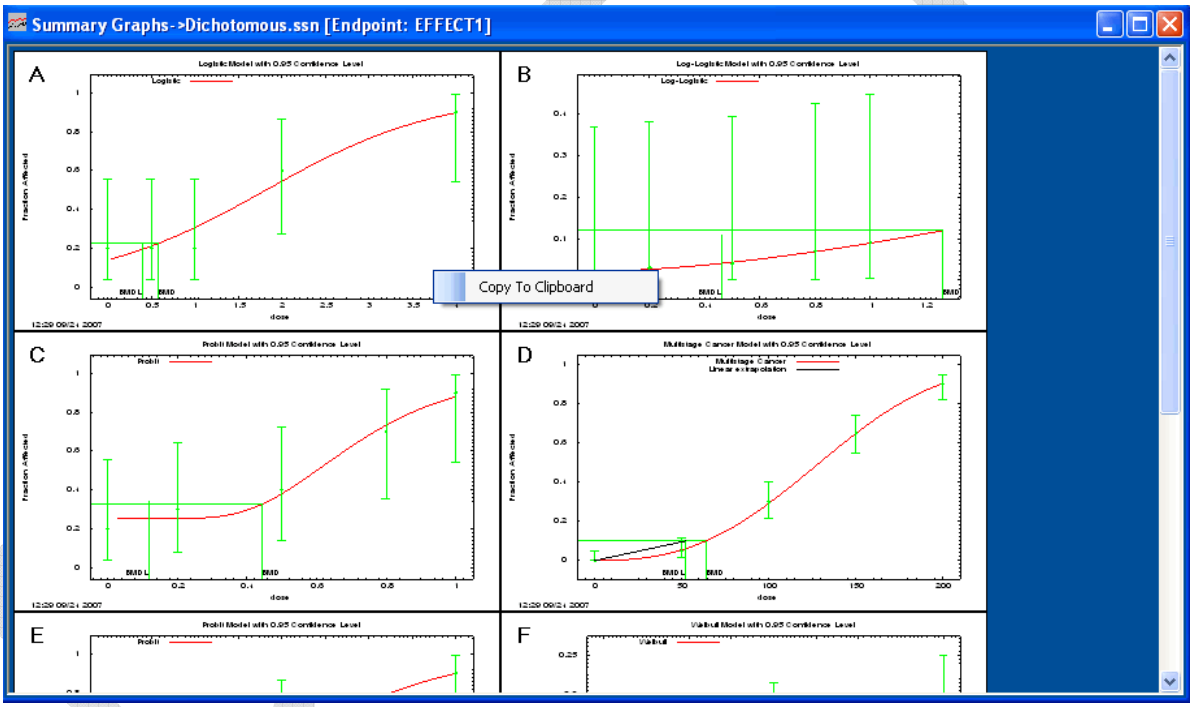
Individual graphs and .OUT File data are displayed when Show Out/Graph is selected by right clicking in the Summary Report window.



Array data is displayed by selecting Display Array Values from the Summary Report window.

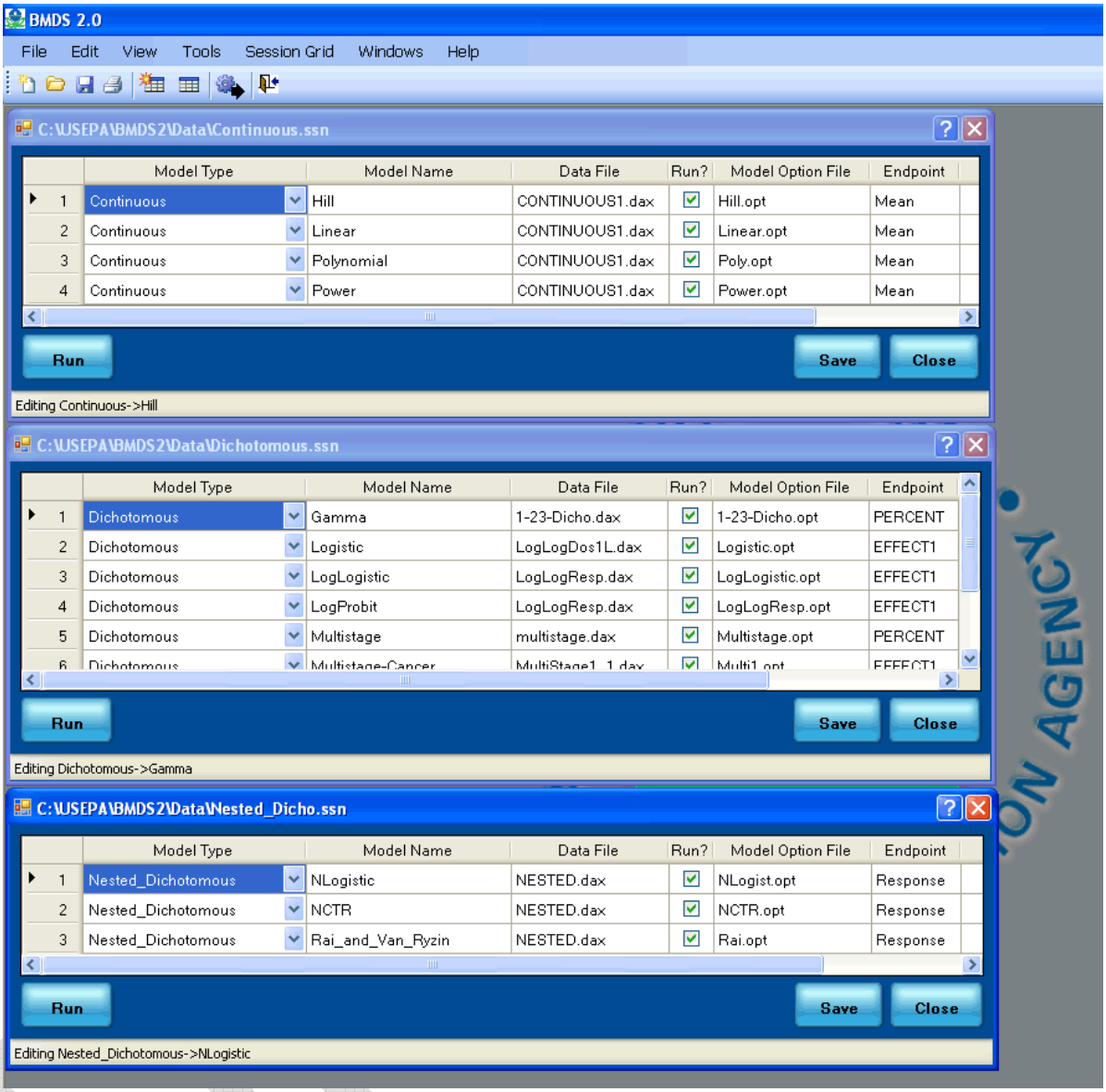


The Summary Graph displays graphs corresponding to each model run. Individual graphs my be copied to the clipboard and inserted into other files such as MS Word documents.



Multiple Sessions

In addition to running a session, BMDS 2.1 is capable of running multiple sessions simultaneously. The results of a session may be computed while computations on a separate session are being run. Simply open multiple sessions and click the **Run** button of each session window.



1.4 New/Open Dataset

The following section will explain the functions of this window, as well as inform the user of the different options presented by the window. A user may run a single model on a single data set by creating a new data set or opening an existing data set in this manner. Analyses pursued in this manner are most similar to the way in which model runs were done in BMDS versions 1.xx.

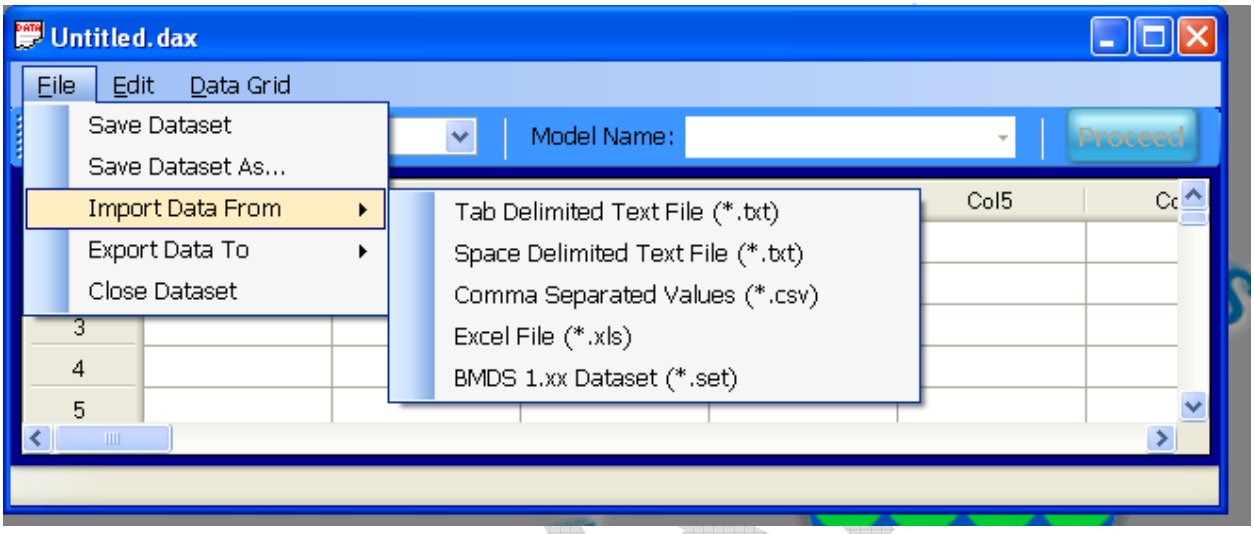
A) Entering Data

Data will already be present in the grid (spreadsheet) if the Open Dataset option was chosen. If the New Dataset option is chosen a blank grid (spreadsheet) will appear allowing the user to manually enter data into the spreadsheet or to paste data from another spreadsheet (e.g., Excel) using most standard spreadsheet operations. **Adding rows or columns** can be accomplished simply by putting data in the cells of the row or column. The default number of rows and columns allowed is 100 and 50, respectively,

but this can be changed on the "Data Grid" tab under "Options …" found under the "Tools" menu item.

When Open Dataset is chosen from the File menu or the Open Dataset button is pressed the user will be prompted for a file to load or import. By default the system initially displays any BMDS dataset files (*.dax) in the "USEPA\BMDS21\Data" directory (i.e., in the folder Data in the folder created when BMDS was installed). These files are in the BMDS format and can be loaded directly.

To import delimited DOS text files or files created in Excel 2003, select New Dataset and then, under the File option on the Data Grid, select Import Data From and selected the type of file you want to import:



Note that: **The first row** of the imported file is reserved for column headers (variable names). Once imported, one can change the name of a column header by clicking with the **right** mouse button the column header (name) and selecting "Rename Column" from the menu. Column headers ***must be one word*** (no spaces allowed).

The Dataset files created by the BMDS program are stored as DOS text files delimited with blanks (i.e., each line will represent a row in the spreadsheet and each blank will signify the start of a new value within the row). If your file is of this format you can choose either "BMDS 1.xx Dataset" if the file has a .set extension or "Space Delimited Text File" from the format menu options. Then the user will have to find the file in the folder in which it is saved on the computer being used (the default directory is again the Data directory where BMDS was installed).

B) Modifying Data

1) Cutting and Pasting

Spreadsheet data can be modified using the keystrokes or Edit menu selections for cut (Ctrl+X), copy (Ctrl+C), paste (Ctrl+V) and Undo (Ctrl+Z) in the normal manner. These operations can also be used to transfer data to and from other spreadsheet applications such as Excel and Lotus. The keystrokes shown below for these operations work in all sections of BMDS, including the Create/Edit spreadsheet.

Undo Paste(Ctrl+Z) Will undo a paste or cut.

Cut (Ctrl+X) Selected data is cut from the spreadsheet

Copy (Ctrl+C) Selected data is copied from the spreadsheet

Paste (Ctrl+V) Cut/copied data is pasted into spreadsheet at cursor location.

Select All Selects the entire spread sheet contents.

2) Adding and Deleting Columns and Rows

Data in columns and rows can be deleted by highlighting the data or the entire column/row (left clicking on its header/label highlights the entire column/row) and hitting the Delete key. Note that when all of the cells in a column/row are empty the column/row is removed when the data set is saved. However, if a column/row contains any data at all, the column/row is retained when the data set is saved.

3) Sorting

Left clicking on the column header will sort the data set by the values in that column. Additional left clicks in the column header will toggle between ascending order and descending order for the sort. If a data field in the selected column is blank the row representing that field will sort to the top of the spreadsheet (regardless of whether the sort order is ascending or descending). You must save your data set after sorting if you want the sort to be retained.

4) Transforming Columns of Data

This is accomplished by clicking with the **right** mouse button in the header of the column where you want the new (transformed) data to appear and selecting "Transform Column" from the menu (see the Data Transformation help section, 1.6, below).

5) Renaming Columns of Data

This is accomplished by clicking with the **right** mouse button in the header of the column where you want the new column name to appear and selecting "Rename Column" from the menu.

C) Saving the Dataset

The dataset file name is shown in the upper left corner of the data grid screen. Newly created data sets are initially assigned a default name of "Untitled." If a model is run on a data set before it is saved to another name, the results of the model run are saved to the root directory of the BMDS program. To save the dataset to a different name and directory location (it is recommended that you save datasets to a unique directory) click on the "Save As" button. If "Save As" is selected, the system will prompt for a filename and a file location. The new file will be saved for future use as a BMDS dataset with a .dax extension (.dax files are actually text files delimited with blanks). If "Save" is selected, changes will be saved to the dataset file name that is in use (i.e., the name that appears in the Selected File window). *Note: All result files (e.g., .out and .plt) from model runs on a single dataset (not when run from a session) are given the same prefix and are saved to the same directory as the .dax file.*

D) Selecting a Model to Run

1) Model Type - Select from six model types:

Continuous,

Dichotomous,

Dichotomous_Alternative,

Nested,

Rptd_Resp_Measures (repeated response measures),_ and

Conc_x_Time (concentration x time).

2) Model - Select from a list of models available for the chosen model type.

E) Model Options / Defining Dataset Variables

When the **Proceed** button is pressed a Model Option Screen appears. That option screen is the one appropriate to the model chosen. From that option screen the user assigns columns in the data set to the required variables and selects the model options (e.g., parameter constraints and BMRF values). Once those choices are complete the user may hit the Run button to complete the analysis of the data set selected.

In the cases where the Model Type is "Rptd Resp Meausures" or "Conc_x_Time," see sections 1.6 and 1.7, respectively, for a description of the option screens and how to complete an analysis. For all other model types, the remainder of this section and Section 2.0 describes how to work with the Option Screens and complete a model run.

All of the variables required for a model must be linked to a column in the spreadsheet. Variables required for running BMDS on a data set will differ according to the Model Type selected, and will appear in the "Column Assignments" section of the Model Option Screen for the model chosen. *For Dichotomous and Dichotomous_Alternative models*, Dose, # Subjects in Dose Group, and Incidence or % Positive columns must be identified. *For Continuous models*, Dose, # Subjects in Dose Group,, Mean and Standard Deviation columns must be identified if response data are reported by dose group. Dose and Response columns must be identified if response data are reported for each individual animal. *For Nested models*, Dose, Litter Specific Covariate, Incidence and Litter Size must be defined. The requirements for a *Rptd_Resp_Measures* or *Conc x Time* model are somewhat different and are discussed in separate sections of this Help Manual.

Dose

Variable representing the amount of a substance an experimental subject consumes (e.g., oral drinking water or food studies), is injected with (e.g., gavage or intravenous injection studies) or is exposed to (e.g., inhalation studies). For inhalation studies, this column would represent the concentration of the substance in the air being inhaled. Most of the time Dose will be an independent variable under the control of the experimenter. However, for epidemiological studies Dose, as well as confounding factors such as age, smoking habits and duration of exposure, are not under the control of the experimenter and may be different for each individual responder. While BMDS allows for the entry and analysis of individual Dose information, provisions for factoring the impact of confounders have not as yet been incorporated.

#Subjects in Dose Group
Independent variable representing the total number of subjects within a dose group for which a continuous Response is measured or dichotomous Incidence is identified.

Incidence
Dependent variable used for Dichotomous and Nested Models to represent the number of subjects within a Dose group responding in a positive, generally considered adverse, manner.

% Positive
Dependent variable used for Dichotomous Models to represent the percent of the total number of subjects within a Dose group that responded positively. The data for this column must be entered as a percent (not a fraction).

Mean
Dependent variable used for Continuous Models to represent the average response within a group (sum of all responses in group divided by Subjects/Group).

Standard Deviation
The positive square root of the variance for a Dose group, which is the sum of the squared deviations of the individual responses from the mean, divided by # Subjects in Dose Group-1.

Response
This dependent variable refers to the individual continuous data responses by subject. If this variable is used, the Subjects/Group, Mean and Standard Deviation continuous data variables are not used and are grayed out.

Litter Size
Number of live pups per litter.

Litter Specific Covariate
This is a covariate such as body weight of dams, number of implants, or litter size that is felt to best explain response variability between litters. It is used in the nested models to try to account for that variability. See Nested Model Descriptions for more details.

As indicated above, when these user-specified choices are completed, and the model options are selected (see the sections below on the options for the specific models) the Run button may be clicked to compete the analysis.

1.5 Data Transformation

As an option in the Create/Edit Dataset window the user has the ability to create a new data column by performing a mathematical operation on existing data fields. To perform a transformation double-click with the **right** mouse button anywhere in the column where the new data will appear. Select "Transform Column." Select an operation from the pull down menu. Select the Column(s) on which the operation will be performed. Enter any operators that may be required. Click OK. The transformed data will appear in the designated column. The following transformations are available.

1) Log Base 10 of a single column

This option will return the Log() base 10 of all values in the selected column.

2) Log Base e (Natural Log) of a single column

This option will return the Log() base e of all values in the selected column.

3) Exponential Base 10 of a single column

This option will return 10 to the x where x is the value in the column for each row in that particular column.

4) Exponential Base e of a single column

This option will return e to the x where x is the value in the column for each row in that particular column.

5) Raise column to Power X

This option will raise each value in a column to a specified Power x, where x is a user specified number.

6) Multiply column by constant X

This option will multiply each value in a column by a specified constant x, where x is a user specified number.

7) Add two columns

This option will return the value of one column added to the value of a second column for each row in that particular column.

8) Subtract two columns

This option will return the value of one column minus the value of a second column for each row in that particular column.

9) Multiply two columns

This option will return the value of one column multiplied by the value of a second column for each row in that particular column.

10) Divide two columns

This option will return the value of one column divided by the value of a second column for each row in that particular column.

11) Quantilize column

This option will return either a 0 or a 1 for all rows based on whether the value in the selected column is Larger or Smaller than a user specified value. If the selected adverse direction is "Larger," a 0 will be returned for values lower and a 1 will be returned for values larger than the user specified value. If the selected adverse direction is "Smaller," a 1 will be returned for values lower and a 0 will be returned for values larger than the user specified value.

12) Add X to column

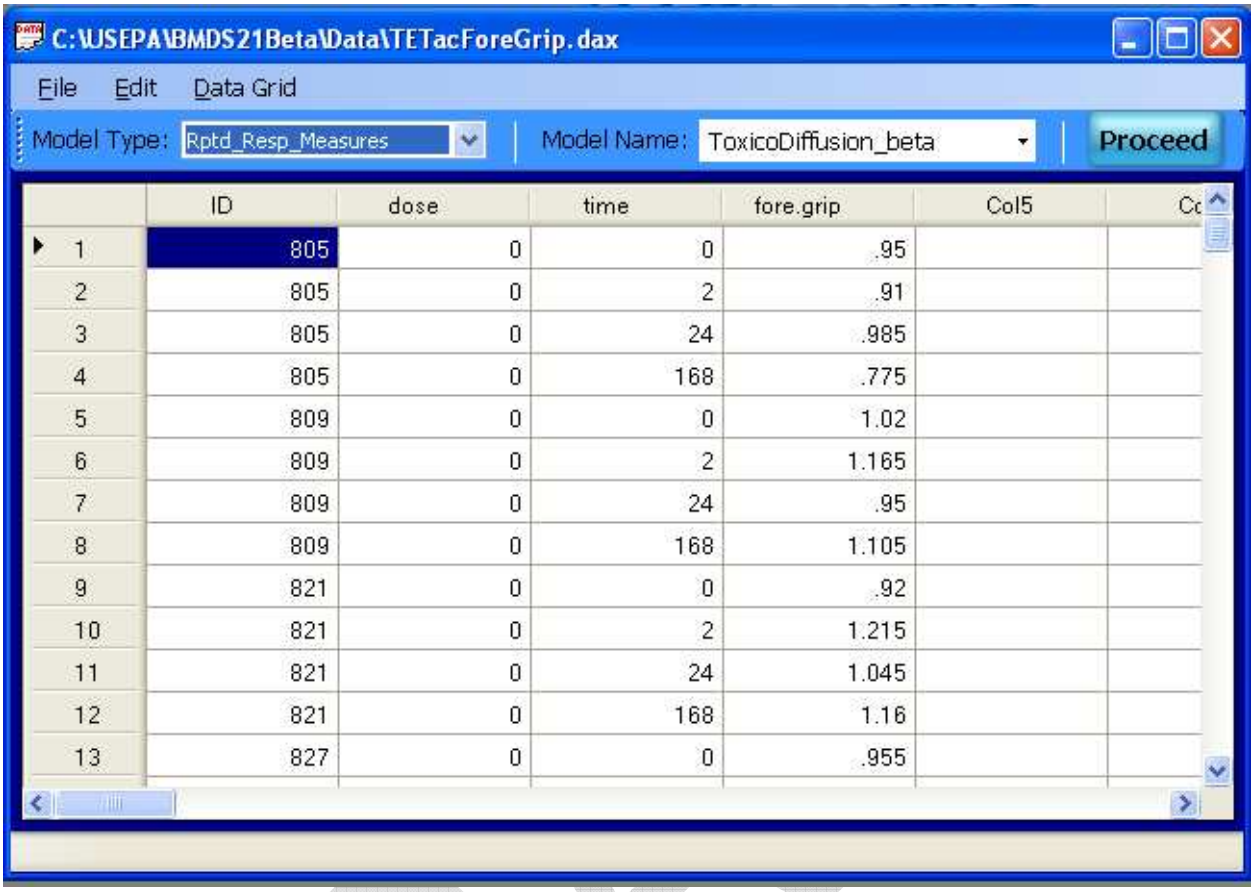
This option will add a constant X to each value in a column, where x is a user specified number.

13) SE to Standard Deviation (SD)

This option will convert standard errors (SE) from a designated column to standard deviations and place them in a designated SD column. The user must also designate the column that contains the number of subjects in each dose group as that value (n) is used in the calculation.

1.6 Repeated Response Measures Data

Once a data set has been created and saved with a name that is not "Untitled" the user can initiate a repeated response measures analysis by selecting the Model Type as "Rptd_Resp_Measures" and hitting the Proceed button. Note that currently there is only one model of this type (the so-called Toxicodiffusion model) so no model selection needs to be done. An example data set for use with the Toxicodiffusion model is shown here:



	ID	dose	time	fore.grip	Col5	Co
1	805	0	0	.95		
2	805	0	2	.91		
3	805	0	24	.985		
4	805	0	168	.775		
5	809	0	0	1.02		
6	809	0	2	1.165		
7	809	0	24	.95		
8	809	0	168	1.105		
9	821	0	0	.92		
10	821	0	2	1.215		
11	821	0	24	1.045		
12	821	0	168	1.16		
13	827	0	0	.955		

Hitting the Proceed button will open a special Option Screen specifically designed to facilitate modeling with the Toxicodiffusion model:

This Option Screen is very similar to that for other BMDS models, so the following information will focus on the unique aspects.

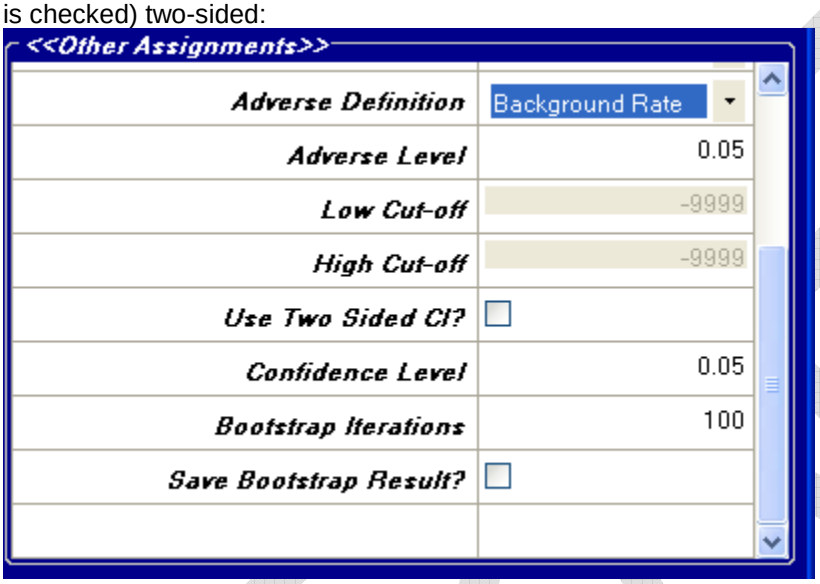
The data for such an analysis will consist of one or more measurements from any given experimental unit (animal) at different times before or after the exposure. Thus, the data set must include a column that identifies which animal the observations come from (the "ID" column in the above example). Even though it is assumed that each animal is exposed to only one dose level, each row of data must include the dose value; the column assignment for that dose value is specified as shown above. The time of each observation (row) must be given (the "time" column in the above example) and the value of the response at that time must be recorded (in the "fore.grip" column in the above example).

There is a section specifying the Plotting Assignments. The properties of the resulting graphs can be identified here.

As with other BMDS model Option Screens, the Parameter Assignments section allows the user to let the program find initial values for the optimization runs (Default – the values "-9999" shown in the option screen are merely flags to pass to the input file that indicate this default option, they are not real initial values) or to initialize the parameter values to values of the user's choice (the "Initialize" option). Currently, the Toxicodiffusion model does not allow users to specify values of the model parameters.

The "Other Assignments" section allows the user to define other important components for the analysis. The time at which exposure occurs (time zero in many experiments) must be specified. So too must the

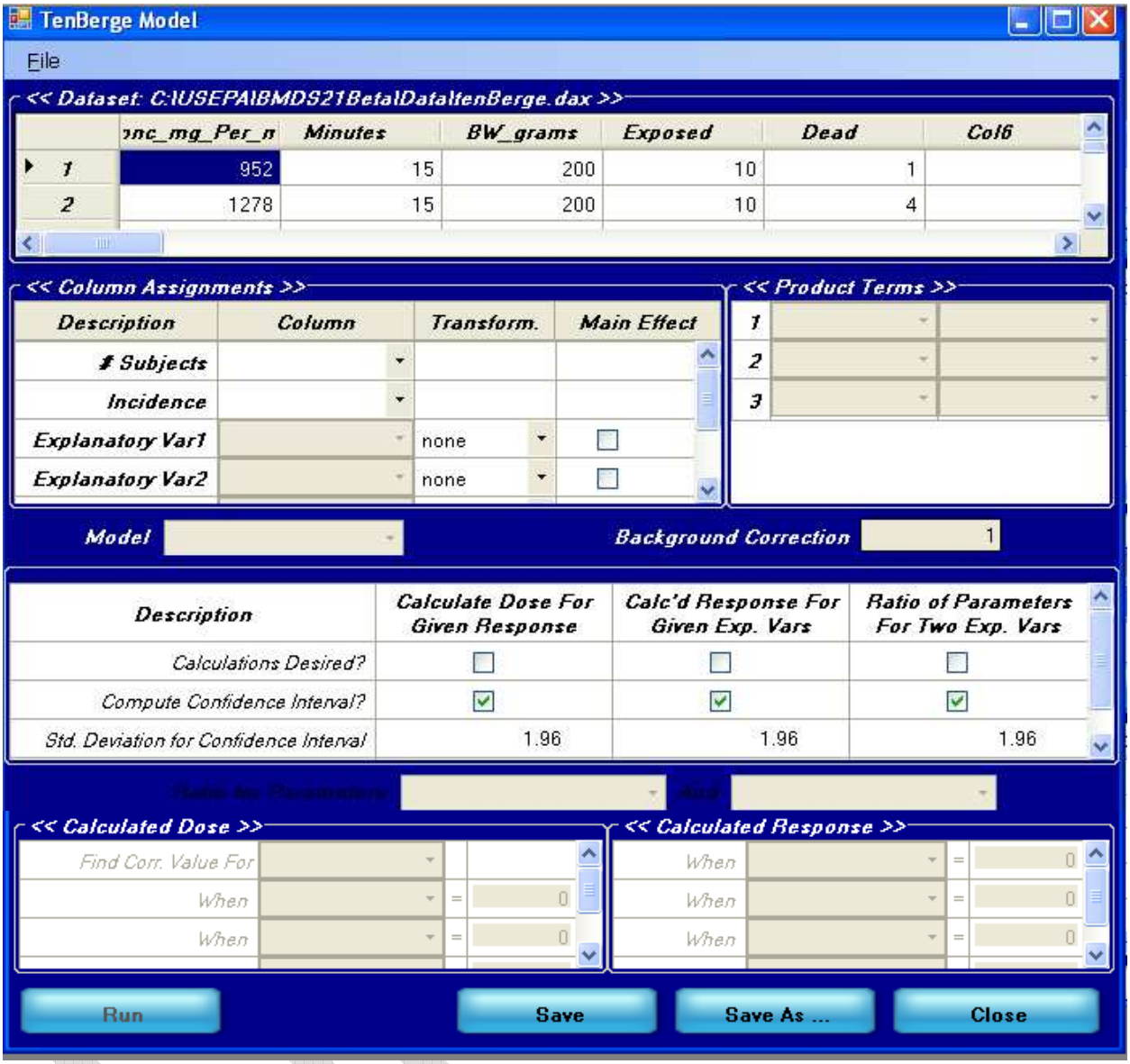
user specify the background degree, which is an integer between 0 and 2 that determines how the responses are assumed to vary *over time* in the absence of exposure. This background (without-exposure) variation is defined by a polynomial of the specified degree (constant, linear, or quadratic for the choices 0, 1, or 2, respectively).
Adverse responses can be defined in one of two ways. Either a background rate of adverse response is specified (e.g., a 5% rate of adverse response in the absence of exposure) or cut-off value(s) can be specified, with the assumption that values above or below (depending on the adverse direction) the cut-off(s) are adverse. The background rate of response need only be defined of the definition is in terms of background rate (probability) of response; the cut-off(s) need only be defined if the definition is in terms of cut point(s).
"Other Assignments" also allows specification of the number of bootstrap iteration to run to estimate confidence bounds. As shown below, those bounds can be one-sided or (if the "Use Two Sided CI?" box is checked) two-sided:



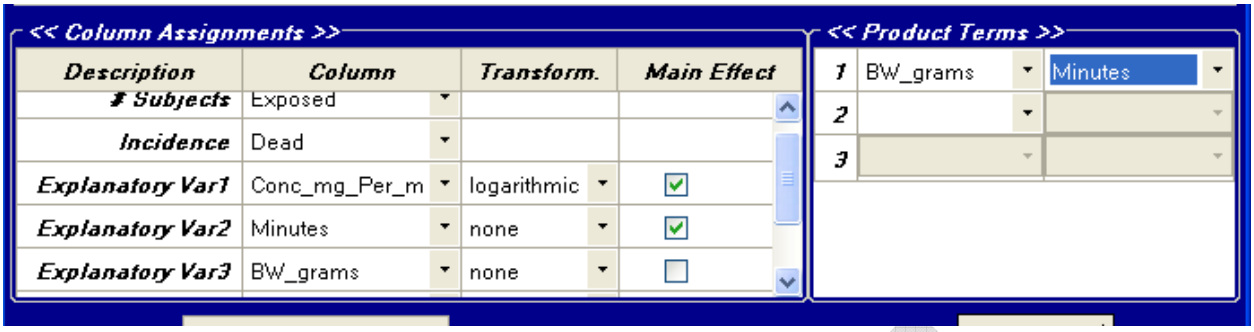
The number of bootstrap iterations should be large enough to provide a stable estimate of the bounds. The value shown above (100) is almost certainly too low for a final, stable estimate of those bounds. Values on the order of 100 or more will probably be required in most cases; the user should perhaps do several runs to determine that the bound estimates have stabilized for the number of iterations chosen. Increasing the number of iterations will noticeably increase the time it takes to run the model.
IMPORTANT NOTE: For the field "Confidence Level" the user must actually enter an α value such that the level of confidence is (1-α)*100%. For example, in the screen shot above, the "Confidence Level field has the value 0.05. This corresponds to requesting 95% confidence limits: (1 – 0.05)*100% = 95%.
Finally, the "Study Description" section is where the user can supply any additional experiment-specific information that s/he wished to have reported in the output files.
Once all the options have been specified as desired, clicking on the Run button will initiate the repeated measures analysis. The run will produce a set of five graphs which will flash momentarily on the screen. when the run is complete the full set of five plots will be available in a summary plot screen. The individual plots can be copied and pasted into other files (e.g., a Word document file).

1.7 Concentration x Time Data

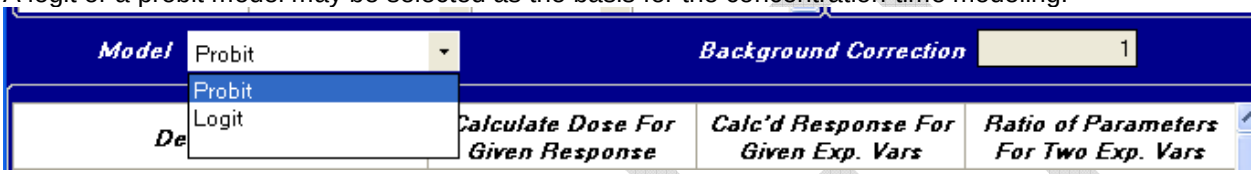
Once a data set has been created and saved with a name that is not "Untitled" the user can initiate an analysis of Concentration/Time data by selecting the Model Type as "Conc_x_Time" and hitting the Proceed button. Note that currently there is only one model of this type (the so-called ten Berge model), so no model selection needs to be done. Hitting the Proceed button will open a special Option Screen specifically designed to facilitate modeling with the ten Berge model:



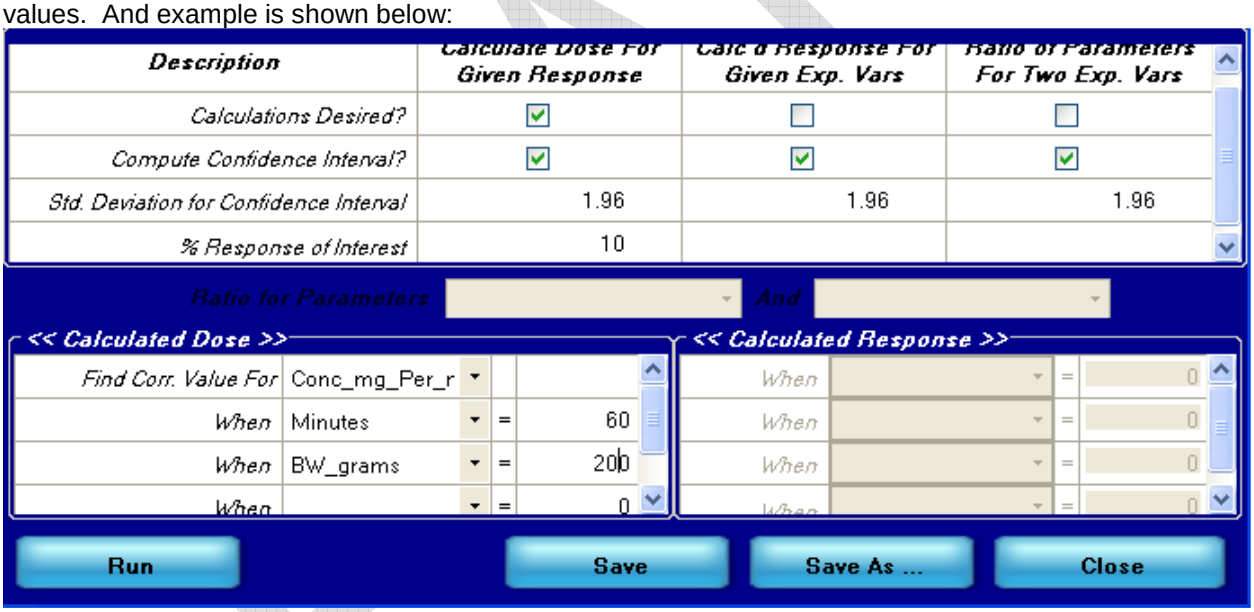
At the top of this Option Screen are the data from the data set that was used to get to this screen. The data should include a variable corresponding to the number in each group ("Exposed" in this example) and the number in each group responding ("Dead" in this example). When the user fills in those two choices in the Column Assignments section of the screen, the remaining column names will appear as possible explanatory variables (Explanatory Var1, etc.) automatically. Currently, there is a limit of five possible explanatory variables. There must be at least two possible explanatory variables; if there is only one possible explanatory variable, the user does not need the Conc_x_Time model – a standard dose-response model from among the Dichotomous or Dichotomous_Alternative model types will suffice.
Not all the possible explanatory variables need be included in the model as main effects or in the product terms. Moreover, explanatory variables included as main effects (by checking the corresponding box in the "Main Effect" column) need not be in the product terms and the product terms need not be restricted to variables included as main effects. One example is shown below:



The variables can be used as is or transformed. The transformations available are the logarithmic (y = Ln(x)) and reciprocal (y = 1/x) transformations. Whatever transformation is chosen will be used everywhere that variable occurs in the specified model (main effect and any product terms).
A logit or a probit model may be selected as the basis for the concentration-time modeling:



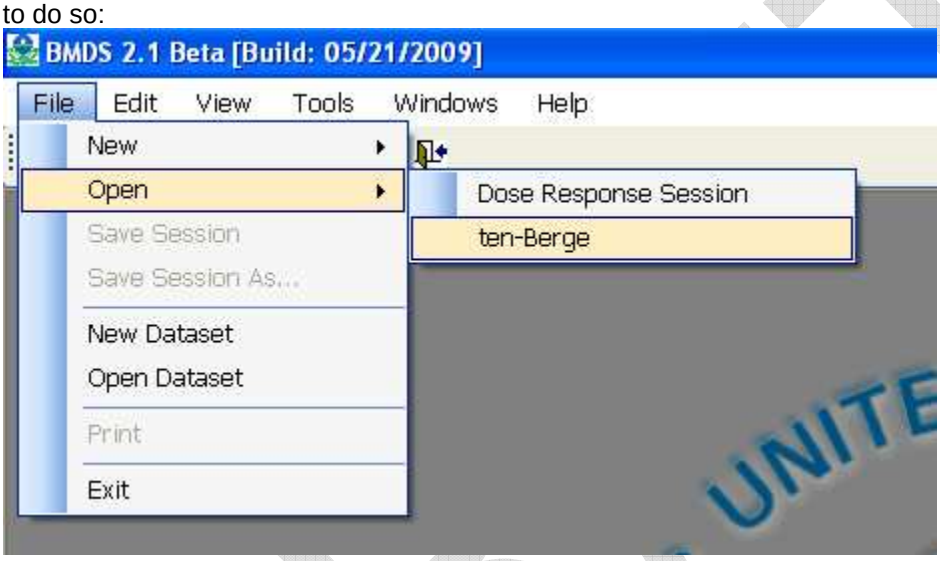
In addition, the user may specify what type of estimates are desired. A BMD type of calculation would correspond to the choice "Calculate Dose for Given Response" where the user specifies a response level (e.g., 10) as a percentage (strictly between 0 and 100) and then requests the valye for one of the explanatory variables included in the model when the other explanatory variables are set to specific values. And example is shown below:



The "Std. Deviation for Confidence Interval can be determined from the table below. Note that this approach was used here because one might often be using a value from a t-distribution rather than a normal distribution. See the documentation for the ten Berge model for additional information.
Table 1: Deviates Corresponding to Confidence Levels of Interest for Confidence Interval Estimation (from Standard Normal Distribution)

α	Confidence Level	Deviate
0.2	80%	1.282
0.1	90%	1.645
0.05	95%	1.960
0.01	99%	2.576

The user can determine the deviate to use for other confidence levels of interest from a table of quantiles of a standard normal distribution, available in many elementary statistics books (or s/he may compute them using Microsoft Excel function "NORMSINV" and putting in (1-α/2) as the argument to that function when interest is in the 100*(1-α) confidence interval).
If the user is more interested in estimates of the response when all the explanatory variables are at specified values or in the ratio of the parameters of given main effects (often considered when concentration and time are logarithmically transformed as a measure of "n," the slope of the response contours on the Ln(conc)-Ln(time) plots). In all of these cases, if the user indicates that such estimates are desired (the appropriate box in the "Calculations Desired?" row is checked by clicking on it), then the cells corresponding to the remaining required fields will no longer be grayed out and values must be entered for all such fields.
Once a ten Berge modeling option screen has been completed, it may be saves using the Save or Save As buttons on the screen. The extension for a ten Berge model run is ".ten" and should be used with all such saves. If, later, the user want to revisit a saved ten Berge analysis, the File menu item can be used to do so:



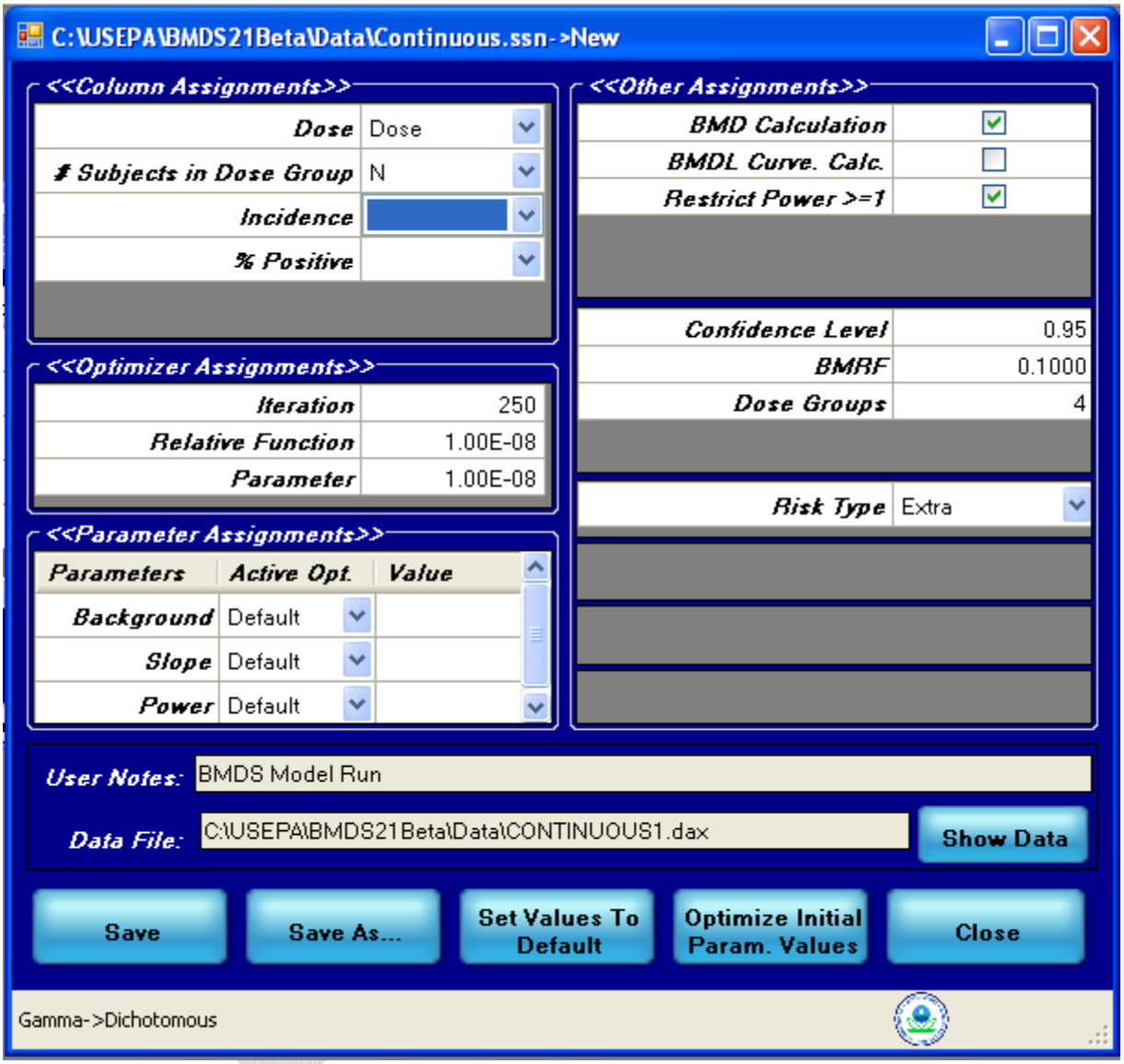
Clicking on the ten-Berge option shown will open a window showing all the ten Berge (.ten) files in the Daya folder of the directory where BMDS was installed. As usual, the user may navigate in that window to the location where the desired ten Berge analysis file is located.

1.8 Software Removal

Users need to uninstall (remove) prior versions of the BMDS 2.1 software before installing a new version to their computer. To uninstall the BMDS application, go to Control Panel, open the Add or Remove Programs utility, select the BMDS 2.1 program in the list, and click on the "Remove" button. Simply deleting the application files doesn't uninstall the software. Note: If the user doesn't have the proper rights in the computer, the "Remove" button will not be shown and the user should uninstall BMDS by re-starting the original setup.exe file and then choosing "Remove Benchmark Dose Software"

2.0 MODEL OPTIONS SCREENS

The Model Option Screen allows users to change options available for a model run. When BMDS is initially run or when the "Reset to Defaults" button is selected all options are set to their default values (identified below). Options chosen and saved in to an Option file (opt extension) will be retained for later use.



Each Model Option Screen contains features which are unique to the model being run. For a discussion of these model specific features see the above Related Topics. All Model Option Screens have the following common features:

Model Type and Name

In the lower left corner of the option screen the name of the specific model being employed and the model type (Dichotomous, Continuous, Nested, Dichotomous-Alternative, or Repeated Response Measures) are displayed.

Data File

A field displaying the name of the data file (*.dax) file.

User Notes

This is an editable field of up to 80 characters in length. The content of this field will be displayed in a single line of text under the date in the *.out file.

Column Assignments Section

This section allows the user to assign columns from the data file to the parameters that are required for model runs.

Optimizer Assignments Section

This section specifies information controling the determination of convergence of the model runs. In general, the user need not be concerned about modifying these values.

Iteration: An upper limit to the number of interations that will be used in the optimizations (default = 250).

Relative Function: This specifies the criterion for ascertaining relative function convergence (default = 1.0e-8)

Parameter Function: This specifies the criterion for ascertaining parameter convergence (default = 1.0e-8)

Parameter Assignments Section

The user can choose one of three options related to parameter values:

Default option: the initial estimated value for a parameter is determined by the program and its value will vary during optimizations;

Specified option: the initial value for a parameter is as specified by the user and its value will remain at that specified value during all optimizations;

Initialized option: the initial estimated value for a parameter is entered by the user but its value will vary during optimizations. *If the initialize option is checked for any parameter, the user must choose the Specified or Initialized option for all parameters.*

Other Assignments Section

This section contains information on parameter constraints and choices for BMD and BMDL calculations. All models contain the following fileds in the Other Assignments section.

BMD Calculation: Specifies whether ot not the user wants a BMD (with associated BMDL) calculated.

BMDL Curve Calc: When this option is selected, the graph resulting from the model run will display a blue BMDL curve. The BMDL curve is estimated by calculating the BMDL for BMDs at BMRs of 1, 5, 10, 20 and 30%, and connecting these points via either a straight line. The calculation of the BMDL curve has been known to cause some convergence problems and can significantly increase computer run time, particularly if several models are being run in a session. Thus, the current default and recommended option is to not request calcuation of the BMDL curve unless absolutely necessary (the BMDL for the requested BMRF will still be estimated and displayed in the output file regardless of the choice for this option).

Confidence Level: The confidence level (default 0.95) associated with the BMDL calculation.

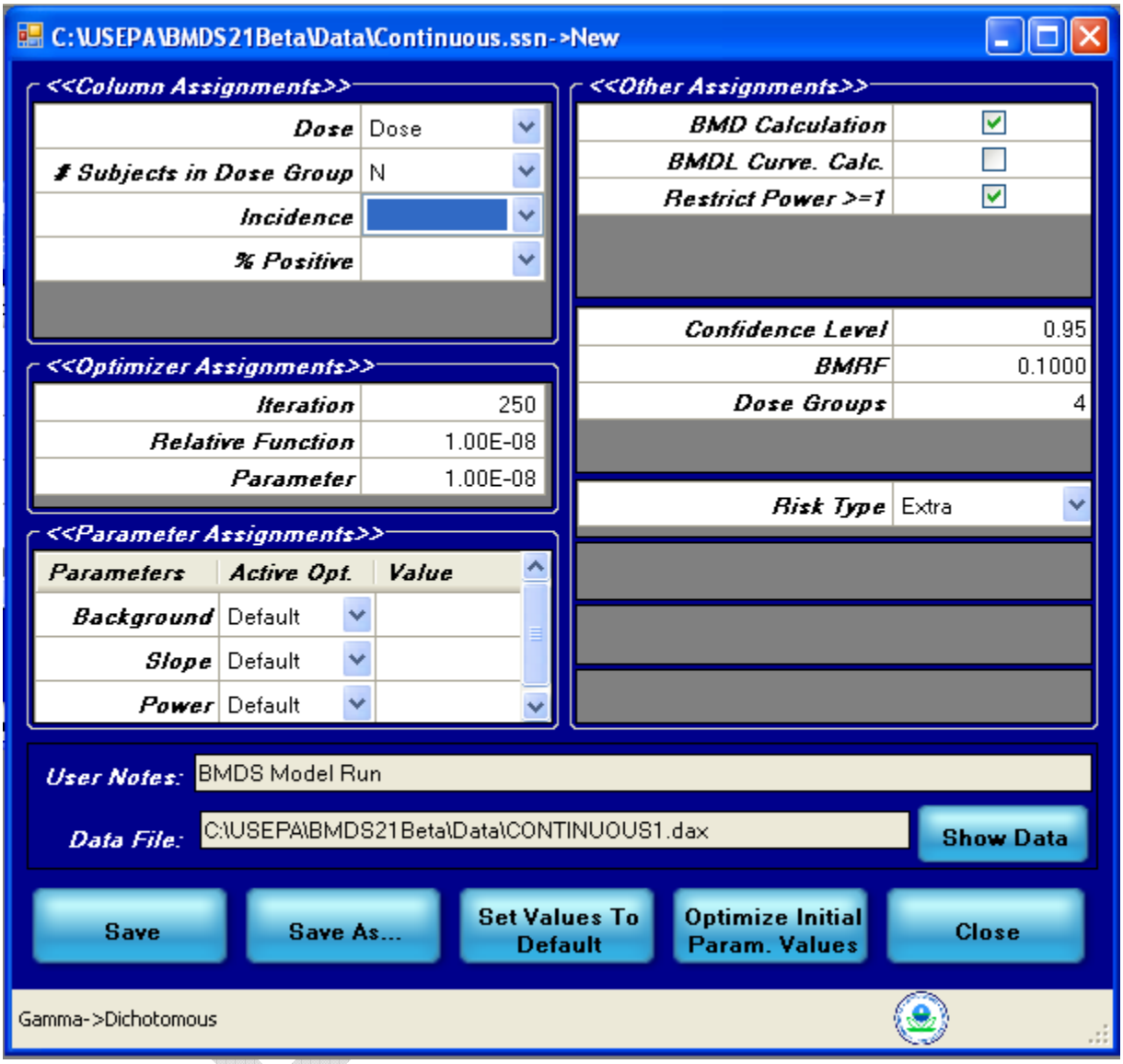
BMRF: The factor defining the benchmark response level. Its value will depend on the Risk Type or BMR Type specified by the user (one of these types will also be in the Other Assignments section, depending on the model type).

Other Buttons

The option file screen also have buttons to Set values to their Defaults, to Save the option file (or "Save As …" if one wants to change the option file name), to Run the model, and to Close the option file screen.

2.1 Dichotomous and Dichotomous_Alternative Model Option Screens

All of the common options described above are available on the Model Option Screens for Dichotomous and Dichotomous_Alternative models. In addition, the following ttw options are available in all Option screens for dichotomous models.



Dose Groups
This is a read-only field indicating the number of Dose groups recorded from the data set file for input into the model.

Risk Type
Choices are "Extra" (Default) or "Added." Added risk is the additional proportion of total animals that respond in the presence of the dose, or the predicted probability of response at dose d, P(d), minus the predicted probability of response in the absence of exposure, P(0). Extra risk is the additional risk divided by the predicted proportion of animals that will not respond in the absence of exposure, 1 - P(0). Thus, extra and additional risk are equal when background rate is zero.

The BMRF for all dichotomous models must be between 0 and 1 (not inclusive).

Note about BMRF and Graphs
The response associated with the BMR that is displayed in the graphical model output will only be the same as the BMR when P(0) = 0. This is because to obtain the actual response value one must solve for P(d) in the equation for added or extra risk discussed above.

In addition to the two options listed above for all dichotomous models, the following options are available for specific models of the Dichotomous or Dichotomous_Alternative Type.

Restrict Slope >= 1
Models: LogLogistic, Log-Probit, Dichotomous-Hill, LogProbit-BgDose

If the slope is allowed to be less than 1, the slope of the dose-response curve is infinite at zero dose.

Restrict Power >= 1
Models: Gamma*,*, Weibull *,* Gamma-BgDose, Weibull-BgDose

Selecting this feature (Default) restricts the power parameter (α) to a value of 1 or greater. If **α < 1**, then the slope of the dose-response curve becomes infinite at the control dose. This may be biologically unrealistic, and can lead to numerical problems when computing confidence limits, so several authors have recommended restricting **α >= 1**.

Degree of Polynomial
Models: Multistage, Multistage-Cancer, Multistage-BgDose, Multistage-Cancer-BgDose

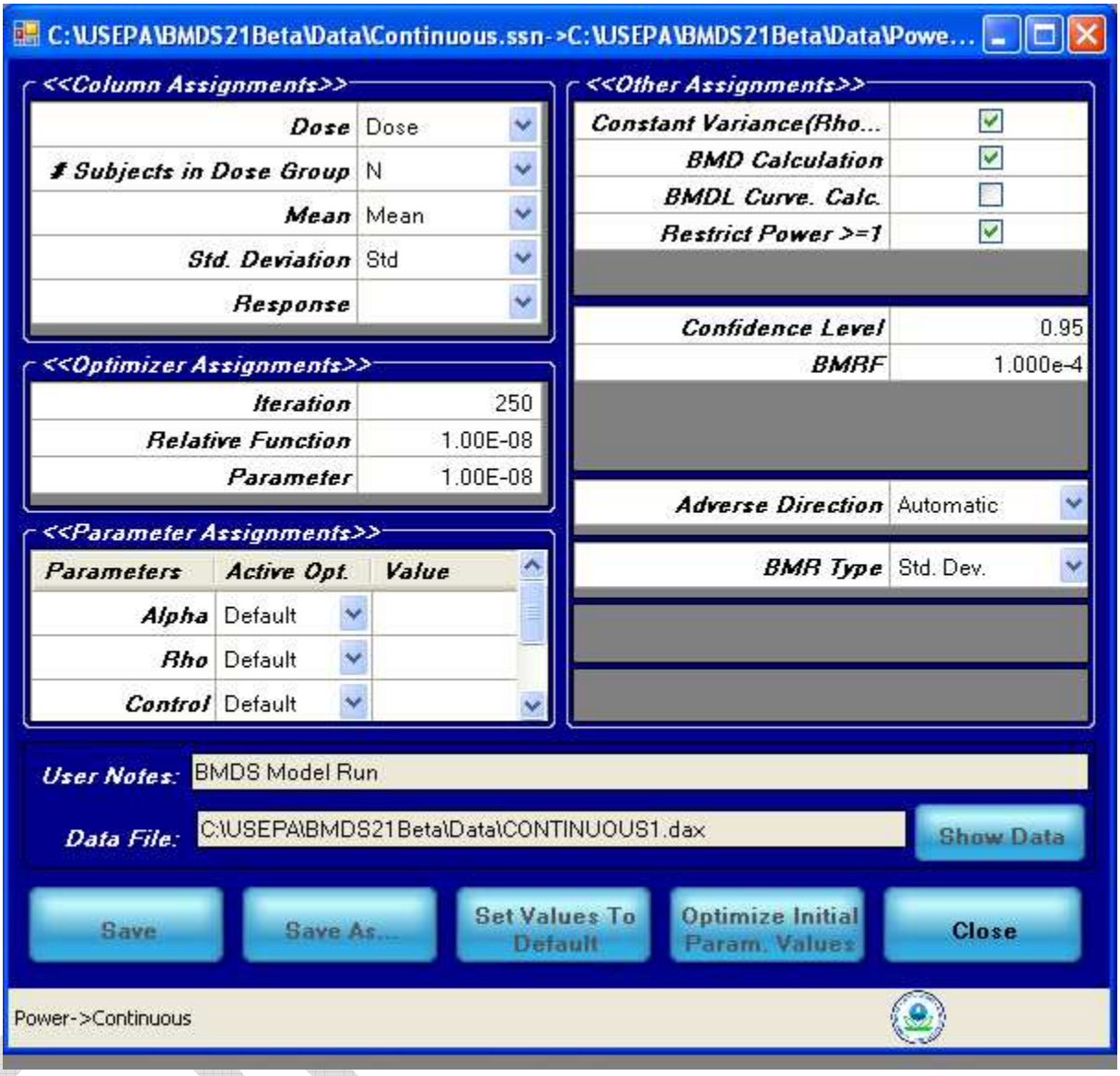
This is the degree of the polynomial model that will be used, or the number of times dose is factored into the model equation (maximum = 23). A value must be entered here before the model will run. Polynomial degree should not exceed the number of dose groups unless the beta coefficients of the model are specified or restricted (beta coefficients are always restricted in the multistage-cancer model).

Restrict Betas >= 0
Models: Multistage, Multistage-BgDose

Selecting this feature (Default) restricts all of the beta (β) parameter coefficients in the multistage model to a value of 0 or greater.

2.2 Continuous Model Option Screens

All of the common options described at the beginning of section 2.0 are available on the Model Option Screens for Continuous models. In addition, the following three options are available in all Option screens for continuous models.



Constant Variance
When selected (Default), the model assumes a constant variance across all dose groups. If not selected, then the model assumes that the variance can be different for each dose group, and varies as a power function of the mean response (see Continuous Model Descriptions for more details).

Adverse Direction
Choices for the Adverse Direction option are "Automatic," (Default), "Up" or "Down." This option refers to whether adversity increases as the dose-response curve rises "up" or falls "down." If automatic is chosen, the software chooses the adverse direction based on the shape of the dose-response curve. Manually choose the adverse direction if you know the direction of adversity for the endpoint being studied. This selection only impacts how the user-designated BMR is used in conjunction with model results to obtain the BMD.

BMR Type
The BMR type is the method of choice for defining the response level used to derive the benchmark dose (BMD). The choices allowed are "Rel. Dev." (Default), "Abs. Dev.," "Std. Dev.," "Point" and "Extra" (*Hill model only*). "Rel. Dev." (Relative Deviation) means the response associated with the BMR will be the background estimate plus or minus (depending on the

Adverse Direction) the product of the background estimate times the BMRF entered by the user. "Abs. Dev." (Absolute Deviation) means the response associated with the BMR will be the background estimate plus or minus the BMRF. "Std. Dev." (Standard Deviation).means the response associated with the BMR will be the background estimate plus or minus the product of the BMRF times the standard deviation for the control group data. "Point" means the response associated with the BMR will be the BMRF value itself. "Extra" (*Hill and some exponential models only*) means the response associated with the BMR will be the background estimate plus or minus the product of the BMRF times the difference between the background estimate and the model estimate of the maximum/minimum response. "Extra" is similar to Extra risk for dichotomous data, except that the maximum (or minimum) achievable response is not 1, but is estimated from the model.

Rel. Dev.Response = $m(0) \pm (BMRF * m(0))$ (*Default*)
Abs. Dev.Response = $m(0) \pm BMRF$
Std. Dev.Response = $m(0) \pm (BMRF * STD)$
Point Response = BMRF
Extra (*Hill and some exponential models only*)

for "up" Response = $m(0) + (BMRF * (m_{max} - m(0)))$
for "down" Response = $m(0) - (BMRF * (m(0) - m_{min}))$

where m(0) is the mean response when exposure equals zero, STD is the standard deviation when exposure equals zero, m_{max} is the maximum predicted mean from the Hill or exponential model, and m_{min} is the minimum predicted mean from the Hill or exponential model.

In addition to the three options listed above for all continuous models, the following options are available for specific continuous models.

Degree Poly
Models: Linear, Polynomial

This is the degree of the polynomial model that will be used, or the number of times dose is factored into the model equation (maximum = 21). A value must be entered here before the model will run. Polynomial degree should not exceed the number of dose groups unless the beta coefficients of the model are restricted. For the linear model, this field is set to 1 and is not editable.

Restrict Power >= 1

Models: Power, Exponential

The power parameter can be restricted to be greater than or equal to one. The power is unrestricted if this option is not selected.

This option is currently disabled for the exponential models.

Restrict n >1

Models: Hill

The n parameter of the Hill model can be restricted to be greater than one. The n parameter is unrestricted if this option is not selected.

Restriction

Models: *Linear, Polynomial*

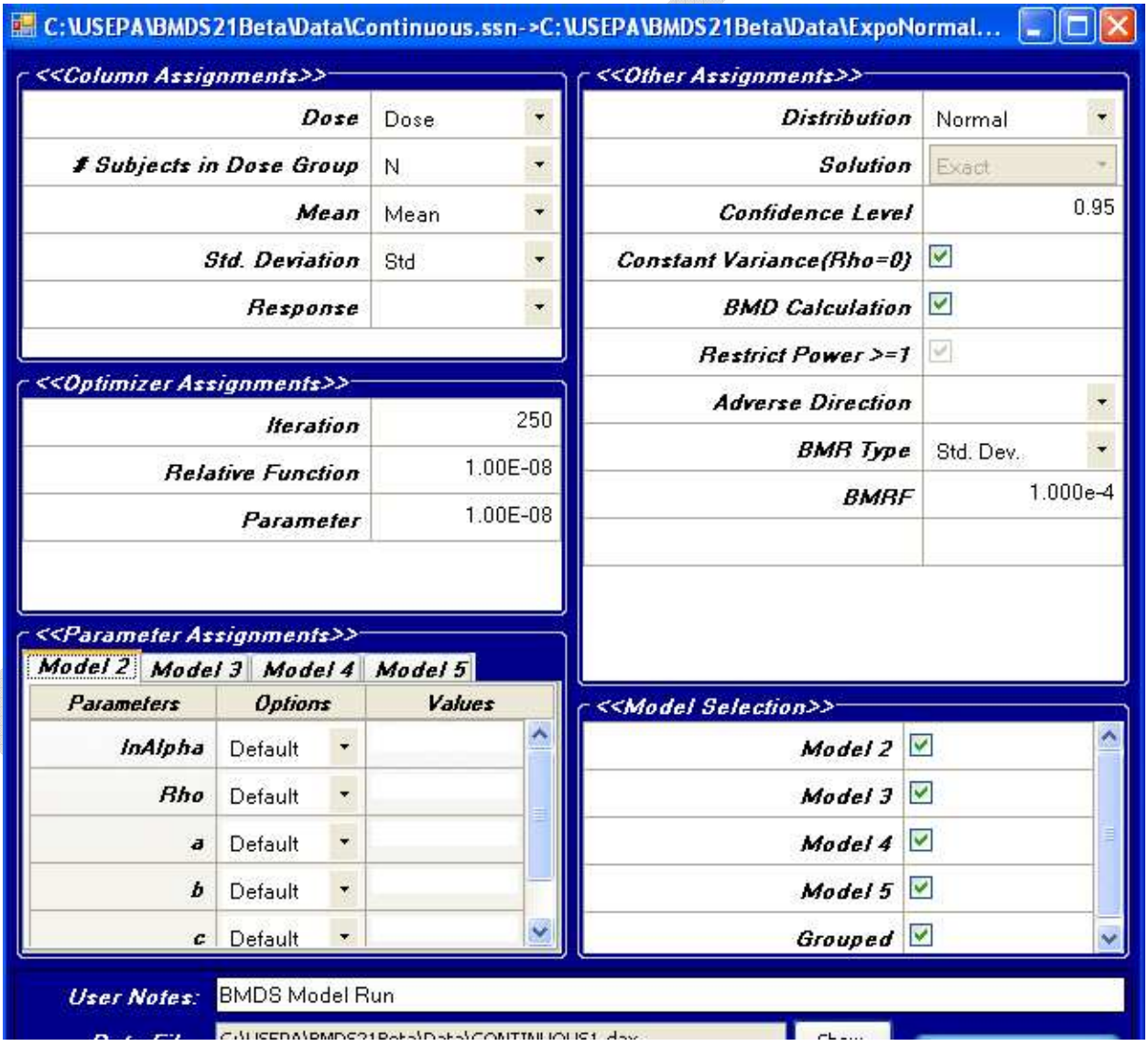
Restrictions on coefficients of the dose terms can be "None" (Default), "Non-negative" (>0), or "Non-positive" (<0). Note that, while no restrictions (None) is the current default for this option, the user should specify that the parameters be restricted to either Non-negative or Non-positive values whenever possible to avoid "wavy" model responses (see details in Polynomial Model description). Since there is only one dose coefficient in the continuous Linear model, this is

sometimes referred to as restricting the slope of this model.

Unique Options for Exponential Models

The exponential model choice actually allows the user to run up to four models that have exponential-dose terms. These models are referred to as exponential Models 2-5 (following a designation by Wout Slob, wherein the restricted (flat) model was model 1). See the section on the definition of the continuous models for additional details.

The user may choose to run any or all of the exponential models when running from a Session screen. (When running on a single data set by use of the data grid – see section 1.4 – all exponential models will be run.) Moreover, the user may select to have the exponential model runs reported (grouped) together in one output file or on separate output files. These choices are made in the "**Model Selection**" section of the exponential model option screen:



Other options unique to the exponential model option screen are as follows:

Distribution: The user may choose to assume that the data are normally or lognormally distributed around the dose-group-specific means. The choice of the distribution affects that type of MLE solution that may be obtained (see next option). Moreover, when a

lognormal distribution is assumed, only constant (log-scale) variance models will be fit to the data; such models correspond to an assumption of a constant coefficient of variation.

Solution: The user may choose to get an exact or approximate MLE solution. When the data are assumed to be normally distributed, the choice is fixed at "Exact" because the exact solution is available no matter how the data are presented (either as group-specific means and variances or as individual responses). When the data are assumed to be lognormally distributed and the data are presented in terms of group-specific means and standard deviations, then the exact MLE solution can not be obtained. In that case, the "Solution" option is fixed at "Approximate" and the means and standard deviations of the log-transformed data are estimated as follows:

log-scale mean = $\ln(\text{mean}) - \ln(1+(\text{std}/\text{mean})^2)/2$
log-scale std = $\text{sqrt}[\ln(1+(\text{std}/\text{mean})^2)]$

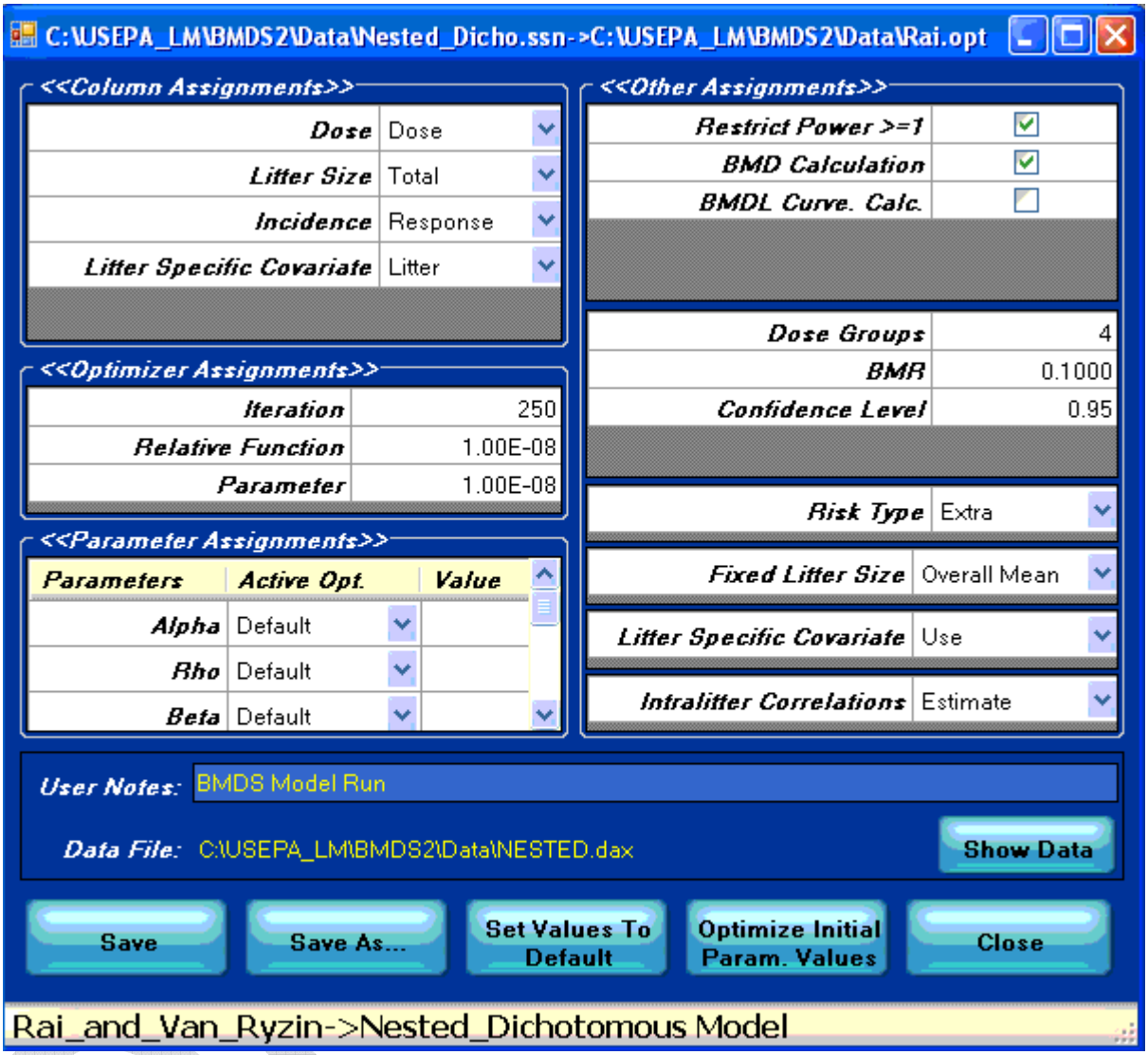
When the data are assumed to be lognormally distributed and the individual responses are available the user may choose between the exact and approximate solutions. In this case, the user is advised to select the exact solution; the only reason to select the approximate solution in this case would be to compare it to other calculations that were done approximately out of necessity.

The "Extra" BMR Type is available for the exponential models. Note, however, that only exponential models 4 and 5 estimate a maximum (or minimum) mean response, so it is only for those two models that extra risk can be defined. If running models 2 and 3 along with models 4 and 5 with the Extra BMR Type, no BMD or BMDL will be calculated for models 2 and 3.

Also note that in the "Parameter Assignments" section, each model has a separate tab to allow model-specific parameter designations (the default, specified, and intialized options discussed above.

2.3 Nested Model Option Screens

All of the common options described at the beginning of section 2.0 are available on the Model Option Screens for Nested models. Note that in the "Column Assignments" section, the parameter "Litter Size" has replaced "#Subjects in Group" and an additional parameter, "Litter Specific Covariate" has been added; these designations reflect the primary use of the nested models, i.e., for modeling data from reporductive or developmental assays in which the number of responders within litters of certain sizes are recorded. The following six options are available in all Option screens for nested models..



Dose Groups
This is a read-only field indicating the number of Dose groups recorded from the data set file for input into the model.

Restrict Power >=1
Power parameter can be restricted to be ≥ 1 (Default)

Risk Type
Choices are "Extra" or "Added." Additional risk is the additional proportion of total animals that respond in the presence of the dose, or the probability of response at dose d, P(d), minus the probability of response in the absence of exposure, P(0). Extra risk is the additional risk divided by the proportion of animals that will not respond in the absence of exposure, 1 - P(0). Thus, extra and additional risk are equal when background rate is zero.

Fixed Litter Size
Choices are "Control Group Mean" (Default) or "Overall Mean." See Nested Model Descriptions for an explanation as to why this option is necessary, and which choice would be preferred for your given data set. Basically, if the Litter Specific Covariate is not affected by dose, the Overall Mean should be used. If the Litter Specific Covariate is affected by dose, consider using the Control Group Mean.

Litter Specific Covariate
Provides user with the option to allow the models to attempt to account for a litter specific covariate or not. If "Use Litter Specific Covariate" is selected (Default), all of the Theta values are estimated . If "Don't Use Litter Specific Covariate" is chosen, all of the Theta values are set to zero.

Intralitter Correlations
Provides user with the option to allow the models to attempt to estimate intralitter correlations or assume they are zero. If "Estimate Intralitter Correlations" is selected (Default), all of the Phi values are estimated (one for each dose group). If "Assume Intralitter Correlations Zero" is chosen, all of the Phi values are set to zero.

3 MODEL DESCRIPTIONS

3.1 Continuous Model Descriptions

Special Considerations for Models for Continuous Endpoints in Simple Designs

Models in this section are for continuous endpoints, such as weight or enzyme activity measures, in simple experimental designs that do not involve nesting or other complications. The models predict the *mean* value of the response, **λ(*dose*)**, expected for a given dose.

Models for continuous endpoints require consideration of more details than do those for dichotomous endpoints in similar designs. While for dichotomous models, we normally model the incidence of adversely affected individuals, and so expect the response to *increase* with increasing dose, in continuous models the change in a measure is modeled without regard for ``adversity'', and the response may increase or decrease. Thus, just what constitutes an adverse change, and how to specify it, must be made explicit. The models in BMDS allow that specification to be made in several ways, which will be described below (BMD Computation).

Another important contrast with dichotomous models is the nature of the probability distribution of response. In dichotomous models, the nature of the experimental design guarantees that the binomial probability distribution is appropriate. There are many more options for continuous distributions, however. In the current version of BMDS, the distribution of continuous measures is assumed to be normal, with the exception of the Exponential Models, for which the user may assume either a normal or a lognormal distribution (see the section on the Lognormal Distribution below). Moreover, for all models and normally distributed data, one may assume either a constant variance (that is, the variance is the same regardless of dose group), or a variance that changes as a power function of the mean value:

$$\sigma_i^2 = \alpha[\mu(dose_i)]^\rho,$$

which is the modeled variance for the *ith* dose group. the expression **λ(*dose*$_i$)** is the observed mean (from the model) for the *ith* dose group, and **α** (alpha) and **ρ (Rho)** are estimated parameters. This formulation allows for several commonly encountered situations. For example, if **ρ** = 2, then the coefficient of variation is constant, a common situation especially for biochemical measures; if **ρ** = 1, then the variance is proportional to the mean, which is sometimes appropriate for large counts (especially if the constant of proportionality, *k*, is 1.0). When a lognormal distribution is assumed, the Exponential Models assume a constant (log-scale) variance, equivalent to a constant coefficient of variation.

Likelihood Function

Suppose there are ***g*** doses,

$$dose_1, \ldots, dose_g$$

with N_i subjects per dose group, and that y_{ij} is the measurement for the j^{th} subject in the ***ith*** dose group. The form of the log-likelihood function depends upon whether the variance is assumed to be constant, or to vary among doses.

For constant variance, the log-likelihood function is:

$$L = -\frac{g}{2}\ln(2\pi) - \sum_{i=1}^{g}\left[\frac{N_i}{2}\ln\sigma_i^2 + \frac{(N_i-1)s_i^2}{2\sigma_i^2} + \frac{N_i\,(\bar{y}_i - \mu(dose_i))^2}{2\sigma_i^2}\right],$$

where

$$s_i^2 = \frac{\sum_{j=1}^{N_i}(y_{ij} - \bar{y}_i)^2}{N_i - 1}$$

is the sample variance for the ***ith*** dose group,

$$\bar{y}_i = \frac{\sum j = 1^{N_i} y_{ij}}{N_i},$$

is the sample mean for the ***ith*** dose group, ***g*** is the number of doses, N_i is the number of subjects in the ***ith*** dose group, and σ^2 the variance which is same in all dose groups. Generally, σ^2 and the parameters hidden here in **λ( )** are to be estimated.

If the variance is allowed to be a power function of the mean, the log-likelihood function is:

$$L = -\sum_{i=1}^{g}\left[\frac{N_i}{2}\ln\alpha + \frac{N_i\,\rho}{2}\ln[\mu(x_i)] + H_i\right]$$

where

$$H_i = \frac{A_i}{2\alpha\,[\mu(dose_i)]^{\rho}} - \frac{B_i}{\alpha\,[\mu(dose_i)]^{\rho-1}} + \frac{N_i}{2\alpha\ [\mu(dose_i)]^{\rho-2}}$$

with

$$\begin{aligned} A_i &= (N_i - 1)s_i^2 + N_i\bar{y}_i^2 \\ B_i &= N_i\ \bar{y}_i. \end{aligned}$$

BMD Computation

In the continuous models, the benchmark dose is always the dose that results in a prespecified change in the mean response. The change can be expressed in several ways

- an absolute change in the mean (Abs. Dev.);
- a change in the mean equal to a specified number of control standard deviations (Std. Dev);
- a specified fraction of the control group mean (Rel. Dev.);
- a specified value for the mean at the BMD (i.e., not a change, but a fixed value) (Point);
- a change equal to a specified fraction of the range of the response, applicable only when the dose-response has an asymptote at high doses (Extra) [Hill and some Exponential models only].

Symbolically, these are (where **δ** represents the BMRF designated by the user):

$$
\begin{aligned}
|\mu(BMD) - \mu(0)| &= \begin{cases} \delta & \text{Abs. Dev.} \\ \delta \cdot \hat{\sigma}_1 & \text{Std. Dev.} \\ \delta \cdot \mu(0) & \text{Rel. Dev.} \end{cases} \\
\mu(BMD) &= \delta \quad \text{Point} \\
\frac{\mu(BMD) - \mu(0)}{\mu_{max} - \mu(0)} &= \delta \quad \text{Extra}
\end{aligned}
$$

BMDL Computation

BMDS currently only calculates one-sided confidence intervals, in accordance with current BMD practice. The general approach to computing the confidence limit for the BMD (called the BMDL here) is the same for all the models in BMDS, and is based on the asymptotic distribution of the likelihood ratio (Crump and Howe, 1985). Two different approaches are followed in these models. In one, the equations that define the benchmark response in terms of the benchmark dose and the dose-response model are solved for one of the model parameters. The resulting expression is substituted back into the model equations, with the effect of reparameterizing the model so that BMD appears explicitly as a parameter. A value for BMD is then found such that, when the remaining parameters are varied to maximize the likelihood, the resulting log-likelihood is less than that at the maximum likelihood estimates by exactly

$$\chi^2_{1,1-2\alpha}/2$$

In the polynomial and exponential models, it is impractical or impossible to explicitly reparameterize the dose-response model function to allow BMD to appear as an explicit parameter. For this model, the BMR equation is used as a non-linear constraint, and the minimum value of BMD is determined such that the log-likelihood is equal to the log-likelihood at the maximum likelihood estimates less

$$\chi^2_{1,1-2\alpha}/2$$

Lognormal Distributions

In previous versions of BMDS, continuous data were always assumed to be normally distributed. In the current version of BMDS, for the exponential models only, the user has the option of specifying that the continuous data being analyzed are lognormally distributed. Lognormal distributions are appropriate only for data that are strictly positive and may be preferable for such data (since the normal distribution allows, in theory, both positive and negative values, no matter what the mean and standard deviation). When a lognormal distribution is specified, the models assume a constant log-scale variance, which is equivalent to an assumption of a constant coefficient of variation (CV).

The likelihood function shown above is then correct for data on the log scale (log-transformed) and is the basis for fitting the log-transformed version of the model in question. That is, if μ_L(dose) is the log-scale mean as a function of dose, the model being fit is μ_L(dose) = ln{m(dose)}, where m(dose) is the specified model (e.g., one of the exponential models parameterized as shown in the section on Exponential Models). Therefore, m(dose) will then be a description of the change in the **median** response as a function of dose since the anti-log of the log-scale mean is the median.

Note: when the input data are summarized in terms of the sample mean and sample standard deviation (or standard error or variance), the exact likelihood of the data can not be determined if the data are lognormally distributed. In such cases, BMDS gives an approximate MLE solution by estimating the log-scale sample mean and log-scale sample standard deviation for each dose group as follows:

estimated log-scale sample standard deviation (s_L): sqrt{ln[1 + s^2/m^2]}
estimated log-scale sample mean (m_L): ln[m] - $s_L^2/2$

where m and s are the reported sample mean and sample standard deviation. When individual responses are available, the user may input those values (where the input dax file will have two columns reporting the dose and the response for each experimental unit) and may request that the exact MLE solution be obtained (which the software does by first log-transforming the individual responses) or that the approximate solution using the estimates shown above be obtained (which the software does by first computing sample means and sample standard deviations). This option allows the user to compare estimates and determine the impact of the approximation or to provide consistency across data sets if some data sets have individual responses while others do not.

3.1.1 Linear Continuous Model Description

Model Form
The Linear model is a form of the polynomial model. The formula for the polynomial model is

$$\mu(dose) = \beta_0 + \beta_1 dose + \beta_2 dose^2 + \cdots + \beta_n dose^n$$

The linear model is a special case of the polynomial model, with ***n*** restricted to 1.

Parameters

Alpha is **α** from the variance model (see Continuous Model Description)

Rho is **ρ** from the variance model (see Continuous Model Description)

Beta0 ... Betan is **β1 ... β*n***; polynomial coefficients.

Special Options

Degree Poly is Degree of polynomial.

Restriction
One of ``None'', ``Non-Positive'', ``Non-Negative''. Determines restrictions on the polynomial coefficients. Restricting them to be either non-positive or non-negative guarantees that the resulting function will be strictly decreasing, strictly increasing, or perfectly flat (when all the coefficients are zero). If the coefficients are unrestricted, more complicated shapes are possible, and, particularly as the degree of the polynomial approaches the number of dose groups minus one, the polynomial will often be quite ``wavy''. When the coefficients are unrestricted and the degree is one less than the number of dose groups (for example, if there are four dose groups, including control, if the degree of the polynomial is three), then the model will exactly reproduce the means of the dose groups.

BMD Computation
The appropriate relationship for the BMR is solved (see Continuous Models: BMD Computation) using numerical methods.

BMDL Computation
The BMR equation (see Continuous Models: BMDL Computation) is used as a non-linear constraint, and the minimum value of BMD is determined such that the log-likelihood is equal to the log-likelihood at the maximum likelihood estimates less

$$\chi^2_{1,1-2\alpha}/2$$

3.1.2 Polynomial Continuous Model Description

Model Form
The formula for the polynomial model is

$$\mu(dose) = \beta_0 + \beta_1 dose + \beta_2 dose^2 + \cdots + \beta_n dose^n$$

Here ***n*** is the degree of the polynomial (labeled ``Degree Poly.'' on the model run screen), and is specified by the user. The linear model is a special case of the polynomial model, with ***n*** restricted to 1.

Parameters

Alpha is **α** from the variance model (see Continuous Model Description)

Rho is **ρ** from the variance model (see Continuous Model Description)

Beta0 ... Betan is **β1 ... β*n***; polynomial coefficients.

Special Options

Degree Poly Degree of polynomial (maximum = 21).

Restriction
One of ``None'', ``Non-Positive'', ``Non-Negative''. Determines restrictions on the polynomial coefficients. Restricting them to be either non-positive or non-negative guarantees that the resulting function will be strictly decreasing, strictly increasing, or perfectly flat (when all the coefficients are zero). If the coefficients are unrestricted, more complicated shapes are possible, and, particularly as the degree of the polynomial approaches the number of dose groups minus one, the polynomial will often be quite ``wavy''. When the coefficients are unrestricted and the degree is one less than the number of dose groups (for example, if there are four dose groups, including control, if the degree of the polynomial is three), then the model will exactly reproduce the means of the dose groups.

BMD Computation
The appropriate relationship for the BMR is solved (see Continuous Models: BMD Computation) using numerical methods.

BMDL Computation
The BMR equation (see Continuous Models: BMDL Computation) is used as a non-linear constraint, and the minimum value of BMD is determined such that the log-likelihood is equal to the log-likelihood at the maximum likelihood estimates less

$$\chi^2_{1,1-2\alpha}/2$$

3.1.3 Power Continuous Model Description

Model Form
The form of the Power model is:

$\mu(dose) = \gamma + \beta \bullet (dose)^{\delta}$

Parameters

Alpha is **α** from the variance model (see Continuous Model Description)

Rho is **ρ** from the variance model (see Continuous Model Description)

Control = γ

Slope = β

Power = δ

Special Options

Restrict power >= 1
Restrict **δ >= 1**. If **δ < 1**, then the slope of the dose-response curve becomes infinite at the control

dose. This may be biologically unrealistic, and can lead to numerical problems when computing confidence limits, so several authors have recommended restricting **δ >= 1**.

BMD Computation
The appropriate relationship for the BMR is solved (see Continuous Models: BMD Computation) analytically.

BMDL Computation
The equations that define the benchmark response in terms of the benchmark dose and the dose-response model are solved for the slope. The resulting expression is substituted back into the model equations, with the effect of reparameterizing the model so that BMD appears explicitly as a parameter. A value for BMD is then found such that, when the remaining parameters are varied to maximize the likelihood, the resulting log-likelihood is less than that at the maximum likelihood estimates by exactly

$$\chi^2_{1,1-2\alpha}/2$$

3.1.4 Hill Continuous Model Description

Model Form
The form of the Hill model is:

$$\gamma + \frac{v \cdot d^n}{k^n + d^n}$$

Parameters

Intercept (Control) = γ

Slope = k

Power = n

Sign = v

Special Options

Restriction
When the "Restrict n > 1" box is checked, the power parameter will be estimated to be greater than or equal to 1.

BMD Computation
The appropriate relationship for the BMR is solved (see Continuous Models: BMD Computation) analytically.

BMDL Computation
The BMR equation (see Continuous Models: BMDL Computation) is used as a non-linear constraint, and the minimum value of BMD is determined such that the log-likelihood is equal to the log-likelihood at the maximum likelihood estimates less

$$\chi^2_{1,1-2\alpha}/2$$

3.1.5 Exponential Beta Continuous Models Description

Introduction

Dr. Wout Slob of RIVM in The Netherlands has proposed a set of nested models known as the exponential models. Currently, these models should be fit only to data having positive (mean) values.

There are four exponential models fit by BMDS and they are defined and labeled as follows.

Model Form

Model 2: $m(dose) = a*\exp\{sign*b*dose\}$
Model 3: $m(dose) = a*\exp\{sign*(b*dose)^d\}$
Model 4: $m(dose) = a*(c - (c-1)*\exp\{-1*b*dose\})$
Model 5: $m(dose) = a*(c - (c-1)*\exp\{-1*(b*dose)^d\})$

[Model 1, as defined by Dr. Slob, is the constant-mean model, called R in BMDS, which is estimated for every continuous data run.] The parameter "sign" is the indicator of the direction of change: +1 for data trending up, -1 for data trending down. It is very important that the user correctly specify the direction of change in the data - for the Exponential Models the "automatic" choice of adverse direction has not been included. Some indicators that the wrong direction has been used for any given run include the observation that one or more models result in a flat curve fit, that optimal solutions for MLE parameters or BMDLs have not been obtained, and/or that the likelihoods associated with the models are much worse than models A1 to A3 (and are more like model R).

Parameters

For all the exponential models the following restrictions apply:

Background Response: a (> 0)
Slope: b (> 0)
Asymptote Parameter: c [Models 4 and 5 only]

c >1 for increasing data
0 < c < 1 for decreasing data

Power: d ($\geq$ 1) [Models 3 and 5 only]

Restrictions

There are no restrictions beyond the parameter constraints shown above for each model.

BMD Computation

The appropriate relationship for the BMR is solved (see Continuous Models: BMD Computation) analytically.

BMDL Computation

The BMR equation (see Continuous Models: BMDL Computation) is used as a non-linear constraint, and the minimum value of BMD is determined such that the log-likelihood is equal to the log-likelihood at the maximum likelihood estimates less

$\chi^2_{1,1-2\alpha}/2$.

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3.2 Dichotomous Model Descriptions

Special Considerations for Models for Dichotomous Endpoints in Simple Designs

BMDS includes in this category models for dichotomous endpoints in which the observations are independent of each other. In these models, the dose-response model provides the probability that an animal will have an adverse response at a given dose. The actual number of animals that have an

adverse response is assumed to be binomially distributed. An example of such a data set is a study in which adult animals are exposed to different concentrations of a toxicant and then evaluated for the presence of liver toxicity. For models for dichotomous endpoints in which the responses are nested (for example, pups in litters, and litters nested within doses), see the section Nested Dichotomous Endpoints.

BMDS contains ten models for dichotomous endpoints (the Probit, Log-Probit, Logistic, Log-Logistic, Weibull, Quantal Linear, Gamma, Multistage, and Multistage-Cancer models). They may all be written in the form:

Prob{*response}* = γ + (1 - γ)*F*(*dose*; α, β, . . .)

Here ***F*(*dose*; α, β, . . .)** is a cumulative distribution function and **γ, α, β, . . .**, are parameters to be estimated using maximum likelihood methods. Sometimes **Prob{*response}*** is written as **P[*dose;* γ**, **α**, **β**, **. . .]** to indicate the relationship between the response probability and the dose as well as parameters. When the function ***F*(*dose*; *α, β*, . . .)** approaches zero as dose approach zero, the parameter **γ** represents the background incidence. In the Logistic and Probit models, ***F*(*0*)** is not zero, unlike in the Log-Logistic and Log-Probit models. In these models, **γ** is set to 0.

Special Options for Models

In addition to the options that are available to all dichotomous models, there may be model-specific options. Generally, these are options to restrict the legal range of a parameter or set of parameters. The range of a parameter may be restricted for two reasons:

- the slope of the dose-response curve becomes infinite at a dose of 0 if the parameter falls below 1, so that the default is to restrain that parameter to be at least 1, or
- the quantal polynomial dose-response curve can become non-monotonic if the coefficients are allowed to be negative, often resulting in the curve looking ``wavy'', so the default is to restrict the coefficients to be non-negative.

The applicable special options are listed in the sections for the specific models.

Likelihood Function

All models in the current version of BMDS are fit using maximum likelihood methods. This section describes the likelihood function used to fit the dichotomous models.

Suppose we employ k doses:

$$dose_1, dose_2, \ldots, dose_k$$

and the total number of s and number of responding s in each dose group are

$$N_1, N_2, \ldots, N_k$$

and, respectively,

$$n_1, n_2, \ldots, n_k$$

The distribution of n_i is assumed to be binomial with probability

$$p_i = p(dose_i; \Theta), i = 1, 2, ..., k$$

where **Θ** is a vector of parameters. Then the log-likelihood function *L* can be written as

$$L = \sum_{i=1}^{k} L_i(N_i, n_i, dose_i; \Theta))$$

where

$$L_i = n_i \ln(p_i) + (N_i - n_i) \ln(1 - p_i), i = 1, 2, \ldots, k.$$

BMD Computation

The BMD is computed as a function of the parameters of the model, which must have already been estimated. The BMDs for dichotomous models are expressed as the dose that would give an (estimated) increase in incidence of x% above the control incidence (where *x* is often in the range of 1 to 10 percent). This increase in incidence is referred to here as the ``BMRF'', for benchmark response factor. Note that, although the word ``response'' is used here, we are really talking about an increase of the incidence over the control incidence (added risk). The actual response associated with the BMR, will only be the same as the BMR when P(0) = 0. This is because to obtain the actual response associated with the BMR one must solve for P(d) in the equation for added or extra risk.

Two formulations for computing the excess over background are in common use, the extra risk model and the additional risk model. In the extra risk model,

$$BMR = \frac{p(BMD; \gamma, \alpha, \beta, \ldots) - p(0; \gamma, \alpha, \beta, \ldots)}{1 - p(0; \gamma, \alpha, \beta, \ldots)}$$

while in the additional risk model,

$$BMR = p(BMD; \gamma, \alpha, \beta, \ldots) - p(0; \gamma, \alpha, \beta, \ldots).$$

The equation appropriate to the risk type formulation that the user requests is solved to get the BMD for a specific model and data set. Details of this computation are included in the descriptions of the models.

BMDL Calculation

BMDS currently calculates one-sided confidence intervals, in accordance with current BMD practice. (Note: the Multistage and Multistage-Cancer models also acalculate one-sided upper confidence limits). The general approach to computing the confidence limit for the BMD (called the BMDL here) is the same for all the models in BMDS, and is based on the asymptotic distribution of the likelihood ratio (Crump and Howe, 1985). Two different approaches are followed in these models. In one, the equations that define the benchmark response in terms of the benchmark dose and the dose-response model are solved for one of the model parameters. The resulting expression is substituted back into the model equations, with the effect of reparameterizing the model so that BMD appears explicitly as a parameter. A value for BMD is then found such that, when the remaining parameters are varied to maximize the likelihood, the resulting log-likelihood is less than that at the maximum likelihood estimates by exactly

$$\chi^2_{1,1-2\alpha}/2$$

In a few models, it is impractical or impossible to explicitly reparameterize the dose-response model function to allow BMD to appear as an explicit parameter. For these models, the BMR equation is used as a non-linear constraint, and the minimum value of BMD is determined such that the log-likelihood is equal to the log-likelihood at the maximum likelihood estimates less

$$\chi^2_{1,1-2\alpha}/2$$

3.2.1 Gamma Model Description

Model Form

The Gamma Model formula is:

$$\text{Prob}\{response\} = p(dose;\gamma,\alpha,\beta) = \gamma + (1-\gamma)\cdot\frac{1}{\Gamma(\alpha)}\int_0^{\beta\, dose} t^{\alpha-1}\mathrm{e}^{-t}dt$$

Here, **0 < γ < 1**, **β >= 0**, and **α > 0** with an option to restrict **α >= 1**.

Parameters

- ``background'' is **γ**
- ``power'' is **α**
- ``slope'' is **β**

Special Options

Restrict power >= 1
Restrict **α >= 1**. If **α < 1**, then the slope of the dose-response curve becomes infinite at the control dose. This is biologically unrealistic, and can lead to numerical problems when computing confidence limits, so several authors have recommended restricting **α >= 1**

BMD Computation

Let

$$G(x;\alpha) = \frac{1}{\Gamma(\alpha)}\int_0^x t^{\alpha-1}\mathrm{e}^{-t}dt$$

be the incomplete Gamma function and

$$G^{-1}(\cdot;\alpha)$$

be its inverse function. Then

$$BMD = \begin{cases} \frac{G^{-1}(BMR;\alpha)}{\beta} & \text{extra risk} \\ \frac{G^{-1}(\frac{BMR}{1-\gamma};\alpha)}{\beta} & \text{additional} \end{cases}$$

BMDL Computation
To calculate the BMDL, the defining equations for the BMD are solved for the slope parameter **β**, which is then replaced in the original model equations. This makes *BMD* appear in the model equations as a parameter. See BMDL Computation in Dichotomous Model Description: for further details.

3.2.2 Logistic Model Description

Model Form

The form of the probability function for the Logistic model is

$$\text{Prob}\{response\} = p(dose; \alpha, \beta) = \frac{1}{1 + \text{e}^{-(\alpha + \beta dose)}}$$

Parameters

- ``intercept'' is **α**
- ``slope'' is **β**

Special Options

- **None**

BMD Computation
The BMD estimate for the Logistic model is defined implicitly by the following equation. An iterative numerical method is used to determine the value of BMD:

$$BMD = -\frac{\ln(\frac{1 - Z}{1 + Z \times \text{e}^{-\alpha}})}{\beta}$$

where

$$Z = \begin{cases} BMR \times \dfrac{1 + \text{e}^{-\alpha}}{\text{e}^{-\alpha}}; & \text{added risk} \\ BMR; & \text{extra risk} \end{cases}$$

BMDL Computation
To calculate the BMDL, the defining equations for the BMD are solved for the intercept parameter **α**, which is then replaced in the original model equations. This makes ***BMD*** appear in the model equations as a parameter. See BMDL Computation in Dichotomous Model Description: for further details.

3.2.3 Log-Logistic Model Description

Model Form
The form of the probability function for the Log-Logistic model is

if *dose* > 0:

$$\text{Prob}\{response\} = p(dose; \gamma, \alpha, \beta) = \gamma + \frac{1 - \gamma}{1 + \text{e}^{-(\alpha + \beta \ln(dose))}},$$

and if *dose* = 0:

$$\text{Prob}\{response\} = p(dose; \gamma, \alpha, \beta) = \gamma;$$

$0 < \gamma < 1$, $\beta >= 0$ (with an option to restrict $\beta >= 1$).

Parameters

- ``background'' is **γ**
- ``intercept'' is **α**
- ``slope'' is **β**

Special Options

- **Restrict slope > 1**: If the slope is allowed to be less than 1, the slope of the dose-response curve is infinite at zero dose.

BMD Computation

The BMD estimate for the Log-Logistic model is:

$$\ln(BMD) = \begin{cases} \frac{\ln\left(\frac{BMR}{1-BMR}\right)-\alpha}{\beta} & \text{extra risk} \\ \frac{\ln\left(\frac{BMR}{1-\gamma-BMR}\right)-\alpha}{\beta} & \text{added risk.} \end{cases}$$

BMDL Computation

To calculate the BMDL, the defining equations for the BMD are solved for the intercept parameter **α**, which is then replaced in the original model equations. This makes ***BMD*** appear in the model equations as a parameter. See BMDL Computation in Dichotomous Model Description: for further details.

3.2.4 Log-Probit Model Description

Model Form
The form of the probability function for the Probit model is
if *dose* > 0:

$$\text{Prob}\{response\} = p(dose;\gamma,\alpha,\beta) = \gamma + (1-\gamma)\Phi(\alpha + \beta\ln(dose)),$$

and if *dose* = 0:

$$\text{Prob}\{response\} = p(dose;\gamma,\alpha,\beta) = \gamma;$$

where

$$\Phi(x) = \int_{-\infty}^{x}\phi(t)dt \quad \text{and} \quad \phi(t) = \frac{1}{\sqrt{2\pi}}\mathrm{e}^{-t^2/2}$$

(that is, **Φ** is the standard normal density function, and **ϕ** is the normal distribution function), **0 < γ < 1, β >= 0** (with an option to restrict **β >= 1**).

Parameters

- ``background'' is **γ**
- ``intercept'' is **α**
- ``slope'' is **β**

Special Options

- Restrict slope > 1: if the slope is allowed to be less than 1, the slope of the dose-response curve is infinite at zero dose.

BMD Computation
The BMD estimate for the Log-Probit model is:

$$\ln(BMD) = \begin{cases} \frac{\Phi^{-1}(BMR)-\alpha}{\beta} & \text{extra risk} \\ \frac{\Phi^{-1}(\frac{BMR}{1-\gamma})-\alpha}{\beta} & \text{added risk.} \end{cases}$$

BMDL Computation
To calculate the BMDL, the defining equations for the BMD are solved for the intercept parameter **α**, which is then replaced in the original model equations. This makes *BMD* appear in the model equations as a parameter. See BMDL Computation in Dichotomous Model Description: for further details.

3.2.5 Multistage and Multistage-Cancer Model Description

Model Form
The Multistage and Multistage-Cancer Model formula is:

$$\text{Prob}\{response\} = p(dose;\gamma,\beta_1,\ldots,\beta_n) = \gamma+(1-\gamma)\cdot(1-\mathrm{e}^{-\sum_{j=1}^{n}\beta_j dose^j})$$

Here, **0 < γ < 1**, and there is an option to restrict **β_i > 0** for all ***i*s.** The degree of the polynomial is *n*. The Multistage-Cancer model is exactly the same as the Multistage model except that the β parameters are always restricted to be positive (the Multistage model allows them to be positive or negative).

Parameters

- **"**Background" is γ
- Dose Coefficients ($Beta_1$ ... $Beta_n$) are β_1 ... β_n

Special Options

Degree Poly
The maximum degree polynomial to fit. (maximum = 23)

Restrict Betas >= 0
When this box is checked, the polynomial coefficients are restricted to be non-negative. This guarantees that the dose-response function will either be perfectly flat or always increasing, with no ``bumps''. This restriction option is not available for the Multistage-Cancer model because it is always implemented for that model.

BMD Computation
There is no general analytic form for the BMD in terms of the BMR and the estimated model parameters for the multistage model. Instead, BMD is the root of the equation

$$\beta_1 BMD + \cdots + \beta_n BMD^n + \ln(1 - A) = 0$$

where

$$A = \begin{cases} BMR & \text{extra risk} \\ \frac{BMR}{1-\gamma} & \text{additional risk} \end{cases}$$

BMDL Computation

The BMR equation is used as a non-linear constraint, and the minimum value of BMD is determined such that the log-likelihood is equal to the log-likelihood at the maximum likelihood estimates less

$$\chi^2_{1,1-2\alpha}/2$$

3.2.6 Probit Model Description

Model Form
The form of the probability function for the Probit model is

$$\text{Prob}\{response\} = p(dose; \gamma, \alpha, \beta) = \Phi(\alpha + \beta dose),$$

and for the Log-Probit model is:

where

$$\Phi(x) = \int_{-\infty}^{x} \phi(t)dt \quad \text{and} \quad \phi(t) = \frac{1}{\sqrt{2\pi}} e^{-t^2/2}$$

(that is, **v** is the standard normal density function, and **Φ** is the normal distribution function), **0 < γ < 1, β >= 0** (with an option to restrict **β >= 1**).

Parameters

- ``background'' is **γ** (Log-Probit only)
- ``intercept'' is **α**
- ``slope'' is **β**

Special Options

- **Log of Dose**: This results in the Log-Probit model.
- **Restrict slope > 1** (Log-Probit only): if the slope is allowed to be less than 1, the slope of the dose-response curve is infinite at zero dose.

BMD Computation
The BMD estimate for the Probit model is defined implicitly by the following equation. An iterative numerical method is used to determine the value of BMD:

$$BMD = \begin{cases} \frac{\Phi^{-1}(BMR[1-\Phi(\alpha)]+\Phi(\alpha))-\alpha}{\beta} & \text{extra risk} \\ \frac{\Phi^{-1}(BMR+\Phi(\alpha))-\alpha}{\beta} & \text{added risk.} \end{cases}$$

BMDL Computation
To calculate the BMDL, the defining equations for the BMD are solved for the intercept parameter **α**, which is then replaced in the original model equations. This makes *BMD* appear in the model equations as a parameter. See BMDL Computation in Dichotomous Model Description: for further details.

3.2.7 Quantal Linear Model Description

Model Form
The Quantal Linear model is a form of the Weibull model. The Weibull Model formula is:

$$\text{Prob}\{response\} = p(dose; \gamma, \alpha, \beta) = \gamma + (1-\gamma)(1 - e^{-\beta\, dose^{\alpha}})$$

The Quantal Linear model results from setting **α** equal to 1 in the Weibull Model.

Parameters

- "Background" is **γ**, restricted to fall in **0 < γ < 1.**
- "Slope" is **β**
- "Power" is **α = 1**

Special Options

None

BMD Computation
The BMD estimate for the Weibull model is:

$$BMD = \begin{cases} \left[\frac{-\ln(1-BMR)}{\beta}\right]^{\frac{1}{\alpha}} & \text{extra risk} \\ \left[\frac{-\ln(1-\frac{BMR}{1-\gamma})}{\beta}\right]^{\frac{1}{\alpha}} & \text{additional risk} \end{cases}$$

BMD estimates for the quantal linear model is found by substituting 1 for **α.**

BMDL Computation
To calculate the BMDL, the defining equations for the BMD are solved for the slope parameter **β**, which is then replaced in the original model equations. This makes *BMD* appear in the model equations as a parameter. See BMDL Computation in Dichotomous Model Description: for further details.

3.2.8 Weibull Model Description

Model Form

The Weibull Model formula is:

$$\text{Prob}\{response\} = p(dose; \gamma, \alpha, \beta) = \gamma + (1-\gamma)(1 - e^{-\beta\, dose^{\alpha}})$$

Note: The Quantal Linear model results from setting **α** equal to 1 in the Weibull Model.

Parameters

- "Background" is **γ**, restricted to fall in **0 < γ < 1.**
- "Slope" is **β**
- "Power" is **α**, and is restricted to **α >= 0** with an option to restrict **α >= 1**.

Special Options

Restrict power >= 1
Restrict **α >= 1**. If **α < 1**, then the slope of the dose-response curve becomes infinite at the control dose. This is biologically unrealistic, and can lead to numerical problems when computing confidence limits, so several authors have recommended restricting **α >= 1**.

BMD Computation
The BMD estimate for the Weibull model is:

$$BMD = \begin{cases} \left[\frac{-\ln(1-BMR)}{\beta}\right]^{\frac{1}{\alpha}} & \text{extra risk} \\ \left[\frac{-\ln(1-\frac{BMR}{1-\gamma})}{\beta}\right]^{\frac{1}{\alpha}} & \text{additional risk} \end{cases}$$

BMDL Computation
To calculate the BMDL, the defining equations for the BMD are solved for the slope parameter **β**, which is then replaced in the original model equations. This makes *BMD* appear in the model equations as a parameter. See BMDL Computation in Dichotomous Model Description: for further details.

3.3 Description of Quantal Models with Background Dose Parameter

Users should consult the Help file for a specific model for details on that model. With a few obvious changes, those details apply also to models with a background dose parameter.

Two Forms of Each Quantal Model

For each of four 'traditional' quantal models in BMDS (multistage, log probit, gamma, and Weibull), alternative models were developed that incorporate a background dose parameter in place of a background response parameter. Such a model was also developed for the log logistic function but is not included in this release for technical reasons[1].

The "cancer model" is a version of the multistage model for which the user cannot relax the restriction on coefficients that requires them to be non-negative, and which reports the "cancer slope factor" (calculated as BMR/BMDL). A new version of this model is provided with a background dose parameter.

The original logistic and probit models (*without* log-transformation of the dose) implicitly allow for a background dose effect, although a background dose parameter is not explicitly estimated. These models do not have a background *response* parameter. Thus, new versions of these models are provided which add an explicit background response parameter γ, increasing the number of parameters from two to three for these new models.

Thus, for each type of quantal model in BMDS, there are now two alternative versions available, one with a background dose parameter and another with a background response parameter.

The alternative forms of model can be represented as follows:

Background response parameter, γ:	$P(\beta, x, \gamma) = \gamma + (1-\gamma)*F\{\beta, x\}$
Background dose parameter, η:	$P(\beta, x, \eta) = F\{\beta, (x+\eta)\}$

Here, F{β, x} represents the functional form specific to each model (multistage, logistic, etc.). F{β, x} is a probability distribution function taking values between 0 and 1 for positive dose values. For more details, see Table 1. In the background dose version of a model, parameter γ is dropped and the parameter η is added.

[1] The log-logistic model with background dose parameter has an especially "flat" log-likelihood surface, making it difficult, for some datasets, for the software to converge to a maximum likelihood solution and especially difficult to solve the BMDL. In general, that model often fails to converge on a BMDL solution when the control response is larger than approximately 0.2 - 0.4.

Table 1. Comparison of current BMDS quantal models with *new models* allowing a background dose or background response parameter

Model Name[1]	Functional Form of the Model	Explicit Background Parameter	Low Dose Linearity ?	# Parameters
Multistage [2]	$\gamma + (1-\gamma)\,[1 - \exp\{-\sum_{j=1}^{k} \beta_j X^j\}]$	γ	Yes if $\beta_1>0$ No if $\beta_1=0$	1+k
multistage_bgd	$1 - \exp\{-\sum_{j=1}^{k} \beta_j (X+\eta)^j\}$	η	Yes	1+k
Logistic	$[1 + \exp\{-(\alpha + \beta X)\}]^{-1}$	None	Yes	2
logistic_bgr	$\gamma + (1-\gamma)\,[1 + \exp\{-(\alpha + \beta X)\}]^{-1}$	γ	Yes	3
Probit	$\Phi\{\alpha + \beta X\}$	None	Yes	2
probit_bgr	$\gamma + (1-\gamma)\,\Phi\{\alpha + \beta X\}$	γ	Yes	3
Log_logistic	$\gamma + (1-\gamma)\,[1 + \exp\{-(\alpha + \beta \log\{X\})\}]^{-1}$	γ	No	3
log_logistic_bgd	$[1 + \exp\{-(\alpha + \beta \log\{X + \eta\})\}]^{-1}$	η	Yes	3
Log_probit	$\gamma + (1-\gamma)\,\Phi\{\alpha + \beta \log\{X\}\}$	γ	No	3
log_probit_bgd	$\Phi\{\alpha + \beta \log\{X + \eta\}\}$	η	Yes	3
Gamma	$\gamma + (1-\gamma)\,[\int_0^{\beta x} t^{\alpha-1} e^{t}\,dt\,] / \Gamma(\alpha)$	γ	No [3]	3
gamma_bgd	$G(\beta(d+\eta), \alpha) / \Gamma(\alpha)$ G is the incomplete gamma function	η	Yes	3
Weibull	$\gamma + (1-\gamma)\,[1 - \exp\{-\beta X^{\alpha}\}]$	γ	No [3]	3
Weibull_bgd	$[1 - \exp\{-\beta (X + \eta)^{\alpha}\}]$	η	Yes	3

1 Names in regular type denote modules (i.e., *.exe files) that currently exist within BMDS. Names in italics denote modules that are new to BMDS and represent alternative forms of the models with a new background parameter.
2 The cancer model is identical to the multistage model except that $\beta \geq 0$ is enforced and the cancer slope factor is reported.
3 If power parameter is > 1, slope → 0 as dose → 0; if power parameter is < 1, slope → ∞ as dose → 0.

Confidence Limits for the Benchmark Dose (BMD)

The new models report both lower and upper confidence limits for the benchmark dose, that is, BMDL and BMDU. The confidence level selected by the user applies to a one-sided confidence limit (as for all the quantal models). Thus, if the user selects a 95% confidence level, "*Confidence level = 0.95*" is reported in the *.out file with the BMD, BMDL, and BMDU. This confidence level applies to a one-sided interval for BMD, e.g., [BMDL, ∞). If the user reports the two-sided interval [BMDL, BMDU], the appropriate confidence level in this example is 90%; in general, if the user selects a confidence level 1-α,

the two-sided interval has confidence level 1-2α.[2]

Parameter Constraints

This section applies to BMDS quantal models generally and is not specific to the new versions of those models. Two sorts of constraints are applicable to the quantal models: natural constraints, which limit parameters to those values permitting $0 \leq P(\text{dose}; \beta, \eta) \leq 1$, and user-selectable constraints. The latter will default to standard settings in BMDS with no need for user actions. Examples of user-selectable constraints are restrictions on the multistage coefficients, which normally are required to be non-negative in order to provide a monotonically increasing dose response function, and a restriction on the power parameter of the gamma and Weibull models, which BMDS requires by default to be no smaller than 1. Natural parameter constraints are shown in Table 2. Advice and observations on user-selectable constraints are provided in the Benchmark Dose Technical Guidance document (on EPA's website "http://cfpub.epa.gov/ncea/" select Publications).

Table 2. Natural parameter constraints in BMDS quantal models.

[2] In some cases, the 2-sided confidence limits may have coverage larger than stated (e.g., greater than 95%), because in some cases they may bound a collection of confidence regions rather than an unbroken interval.

Model Name[1]	Functional Form of the Model	Parameter Constraints
Multistage[2]	$\gamma + (1-\gamma)\,[1 - \exp\{-\sum_{j=1}^{k} \beta_j X^j\}]$	$0 \le \gamma \le 1$
multistage_bgd[2]	$1 - \exp\{-\sum_{j=1}^{k} \beta_j (X+\eta)^j\}$	$\eta \ge 0$
Logistic	$[1 + \exp\{-(\alpha + \beta X)\}]^{-1}$	$-\infty < \alpha < +\infty$, $\beta \ge 0$
logistic_bgr	$\gamma + (1-\gamma)\,[1 + \exp\{-(\alpha + \beta X)\}]^{-1}$	$-\infty < \alpha < +\infty$, $\beta \ge 0$ $0 \le \gamma \le 1$
Probit	$\Phi\{\alpha + \beta X\}$	$-\infty < \alpha < +\infty$, $\beta \ge 0$
probit_bgr	$\gamma + (1-\gamma)\,\Phi\{\alpha + \beta X\}$	$-\infty < \alpha < +\infty$, $\beta \ge 0$ $0 \le \gamma \le 1$
Log_logistic	$\gamma + (1-\gamma)\,[1 + \exp\{-(\alpha + \beta \log\{X\})\}]^{-1}$	$-\infty < \alpha < +\infty$, $\beta \ge 0$ $0 \le \gamma \le 1$
log_logistic_bgd	$[1 + \exp\{-(\alpha + \beta \log\{X + \eta\})\}]^{-1}$	$-\infty < \alpha < +\infty$, $\beta \ge 0$ $\eta \ge 0$
Log_probit	$\gamma + (1-\gamma)\,\Phi\{\alpha + \beta \log\{X\}\}$	$-\infty < \alpha < +\infty$, $\beta \ge 0$ $0 \le \gamma \le 1$
log_probit_bgd	$\Phi\{\alpha + \beta \log\{X + \eta\}\}$	$-\infty < \alpha < +\infty$, $\beta \ge 0$ $\eta \ge 0$
Gamma	$\gamma + (1-\gamma)\,[\int_0^{\beta x} t^{\alpha-1} e^{t}\,dt\,] / \Gamma(\alpha)$	$\alpha > 0$, $\beta \ge 0$ $0 \le \gamma \le 1$
gamma_bgd	$G(\beta(d+\eta), \alpha) / \Gamma(\alpha)$ G is the incomplete gamma function	$\alpha > 0$, $\beta \ge 0$ $\eta \ge 0$
Weibull	$\gamma + (1-\gamma)\,[1 - \exp\{-\beta X^{\alpha}\}]$	$\alpha > 0$, $\beta \ge 0$ $0 \le \gamma \le 1$
Weibull_bgd	$[1 - \exp\{-\beta (X + \eta)^{\alpha}\}]$	$\alpha > 0$, $\beta \ge 0$ $\eta \ge 0$

1 Names in regular type denote modules (i.e., *.exe files) that currently exist within BMDS. Names in italics denote modules that are new to BMDS and represent alternative forms of the models with a new background parameter.
2 The cancer model is identical to the multistage model except that $\beta_j \ge 0$ is enforced and the cancer slope factor is reported.

In some cases, BMDS software will report that a parameter has "*... hit a bound implied by some inequality constraint and thus has no standard error.*" In that case, the printed parameter estimate will equal some natural or user-selectable constraint (for example, $\beta = 0$ for multistage, or power $\alpha = 1$ for gamma[3]). In

[3] There is also an arbitrary upper bound of 18 for the power parameter for the gamma and Weibull models

such cases, the Wald confidence intervals for the other parameters are not even asymptotically correct.[4] The 2-sided profile-likelihood confidence intervals for the BMD and Extra or Added Risk are asymptotically correct in such cases.[5] (However, whether or not a boundary has been 'hit', a 1- sided profile-likelihood confidence interval may not have the nominal coverage - if the nominal coverage is 1-α, the asymptotic coverage for BMDL could be anything between 1 and 1-2α.)

Also, if the power parameter for the gamma or Weibull models is reported equal to 18 and the warning "*... hit a bound ...* " appears, the parameter estimates are maximum likelihood estimates only in the restricted sense that the power parameter has been assigned a value and the other parameters are MLEs conditional on that assigned value. Such model results are not strictly comparable with others in terms of AIC. In such a case, the BMD and BMDL could depend on the choice of power parameter; thus, sensitivity analysis is indicated if one intends to rely on the reported BMD or BMDL.

Origin and Properties of Background Parameters

The background response parameter has been said to represent "... independent action between the chemical and the background." (NRC, 1980), or, in the case of cancer, "...carcinogens that cause a response of cancer in a way that is completely independent of the mechanisms by which the primary carcinogen causes a response." (Crump et al., 1976). Thus, it has also been called an independent background (Crump et al., 1976; Hoel, 1980). The background dose parameter has been said to represent additivity between the applied dose of a chemical and the background (NRC, 1980), or to represent "... carcinogens (including spontaneous biochemical accidents) that somehow act in conjunction with the primary carcinogen ..." (Crump et al., 1976). Thus, it has also been termed an additive background (Crump et al., 1976; Hoel, 1980).

Models with a background dose parameter will have an approximately linear response to dose at very low doses (Crump et al., 1976). Only some of the original quantal models will behave in this way (see Table 1). The specification of the background term can have a substantial influence over risk estimates made well below the range of experimental doses (Krewski and van Ryzin, 1981; NRC, 1980). The original logistic and probit models (*without* log-transformation of the dose) implicitly allow for a background dose effect, although a background dose parameter is not explicitly estimated, and these models exhibit low-dose linearity. The new versions of these models provide an explicit background response parameter, and also exhibit low-dose linearity.

Table 1. Comparison of current BMDS quantal models with *new models* allowing a background dose or background response parameter

[4] See G. Molenberghs and G. Verbeke (2007) American Statistician 61: 22-27; B. Sinha et al. technical report at http://www.math.umbc.edu/~kogan/technical_papers/index2007.html.; Self, S.S. and K-Y. Liang (1987) Asymptotic properties of maximum likelihood estimators and likelihood ratio tests under nonstandard conditions, J.Am. Stat. Assoc. 82: 605-610.

[5] B. Sinha et al. technical report at http://www.math.umbc.edu/~kogan/technical_papers/index2007.html.

Model Name[1]	Functional Form of the Model	Explicit Background Parameter	Low Dose Linearity ?	# Parameters
Multistage [2]	$\gamma + (1-\gamma)\,[1 - \exp\{-\sum_{j=1}^{k} \beta_j X^j\}]$	γ	Yes if $\beta_1>0$ No if $\beta_1=0$	1+k
multistage_bgd	$1 - \exp\{-\sum_{j=1}^{k} \beta_j (X+\eta)^j\}$	η	Yes	1+k
Logistic	$[1 + \exp\{-(\alpha + \beta X)\}]^{-1}$	None	Yes	2
logistic_bgr	$\gamma + (1-\gamma)\,[1 + \exp\{-(\alpha + \beta X)\}]^{-1}$	γ	Yes	3
Probit	$\Phi\{\alpha + \beta X\}$	None	Yes	2
probit_bgr	$\gamma + (1-\gamma)\,\Phi\{\alpha + \beta X\}$	γ	Yes	3
Log_logistic	$\gamma + (1-\gamma)\,[1 + \exp\{-(\alpha + \beta \log\{X\})\}]^{-1}$	γ	No	3
log_logistic_bgd	$[1 + \exp\{-(\alpha + \beta \log\{X + \eta\})\}]^{-1}$	η	Yes	3
Log_probit	$\gamma + (1-\gamma)\,\Phi\{\alpha + \beta \log\{X\}\}$	γ	No	3
log_probit_bgd	$\Phi\{\alpha + \beta \log\{X + \eta\}\}$	η	Yes	3
Gamma	$\gamma + (1-\gamma)\,[\int_0^{\beta x} t^{\alpha-1} e^{-t}\,dt\,] / \Gamma(\alpha)$	γ	No [3]	3
gamma_bgd	$G(\beta(d+\eta), \alpha) / \Gamma(\alpha)$ G is the incomplete gamma function	η	Yes	3
Weibull	$\gamma + (1-\gamma)\,[1 - \exp\{-\beta X^{\alpha}\}]$	γ	No [3]	3
Weibull_bgd	$[1 - \exp\{-\beta (X + \eta)^{\alpha}\}]$	η	Yes	3

1 Names in regular type denote modules (i.e., *.exe files) that currently exist within BMDS. Names in italics denote modules that are new to BMDS and represent alternative forms of the models with a new background parameter.
2 The cancer model is identical to the multistage model except that $\beta \geq 0$ is enforced and the cancer slope factor is reported.
3 If power parameter is ≥ 1, slope → 0 as dose → 0; if power parameter is < 1, slope → ∞ as dose → 0.

Model Behavior in Relation to Background Parameter

The effects of the two sorts of background parameters, γ and η, are illustrated for the log-probit models:

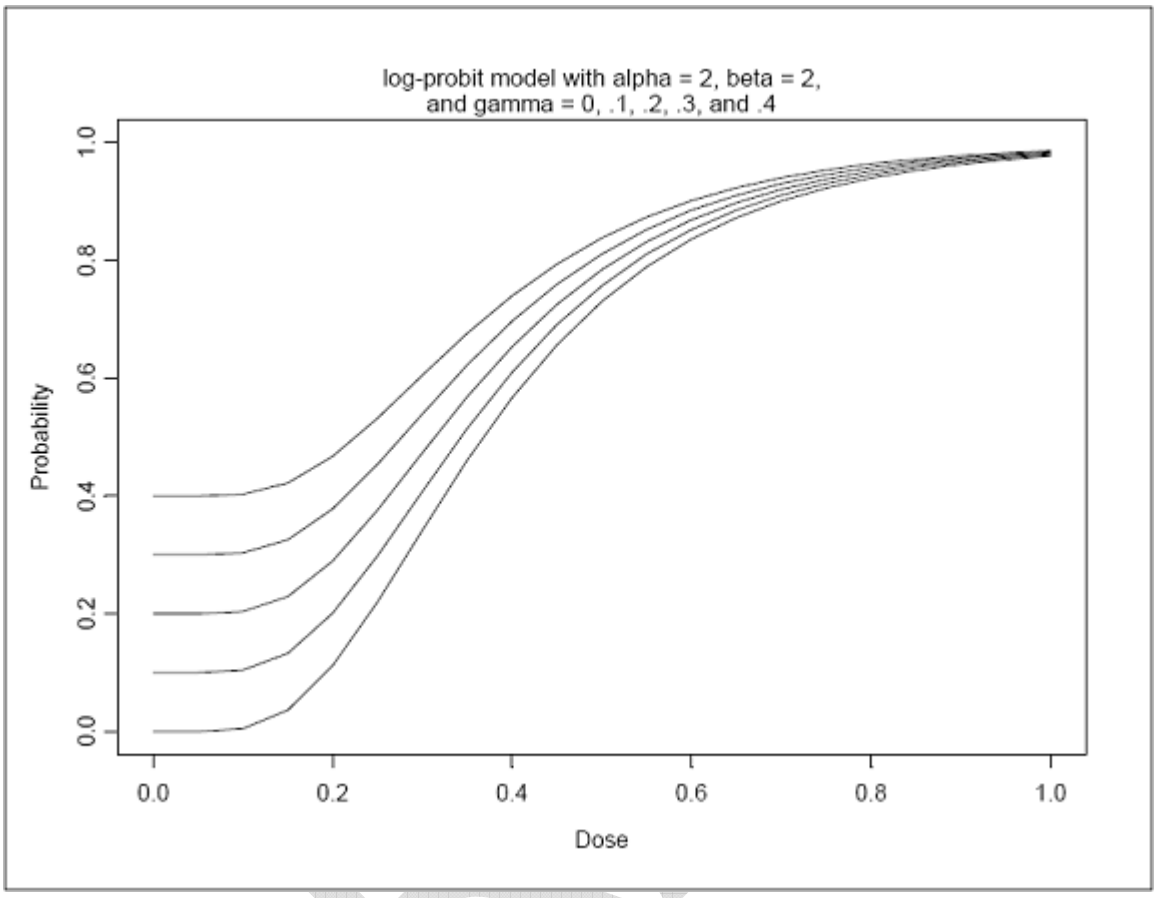
$$P(\text{dose}; \gamma, \alpha, \beta) = \gamma + (1-\gamma)\,\Phi(\alpha + \beta \log\{X\})$$

$$P(\text{dose}; \eta, \alpha, \beta) = \Phi(\alpha + \beta \log\{X + \eta\})$$

Models with a background response parameter can represent the functional shape of F(dose; β) starting from a "floor" at P(0) = γ (Figure 1). The response curve may appear sigmoidal, concave ("supralinear"),

convex ("sublinear") or nearly linear, depending on the values of the other parameters.

Figure 1. Log-probit model with background response term, P(dose; γ, α, β) = γ + (1-γ) Φ{α + β*log(X)}. Here α = 2, β = 2, and γ is varied from 0 to 0.4.



Models with a background parameter additive to dose (η) can shift the response curve left or right (Figure 2), for fixed α (intercept) and β (slope). The background dose model can successfully fit datasets that appear concave ("supralinear"), appearing as if the response had been truncated on the left. Figure 2 also suggests that the background dose model may have difficulty fitting a convex or sigmoidal data pattern that begins with a high control response, but may be successful in fitting a linear to concave (supralinear) response that begins with a high response at zero dose. (In this Figure, the other two parameters are fixed; however, experience with maximum likelihood fitting of various datasets suggests that these qualitative generalizations are correct).

Figure 2. Log-probit model with background dose term. The background-dose parameter (η) was varied, taking values of 3 to 0 from left to right. For this plot, α = -0.1 and β = 1. This illustrates how increasing the background dose parameter shifts the response curve leftward (observed doses would of course be non-negative; the horizontal axis was extended to negative doses to illustrate the functional forms of these models).

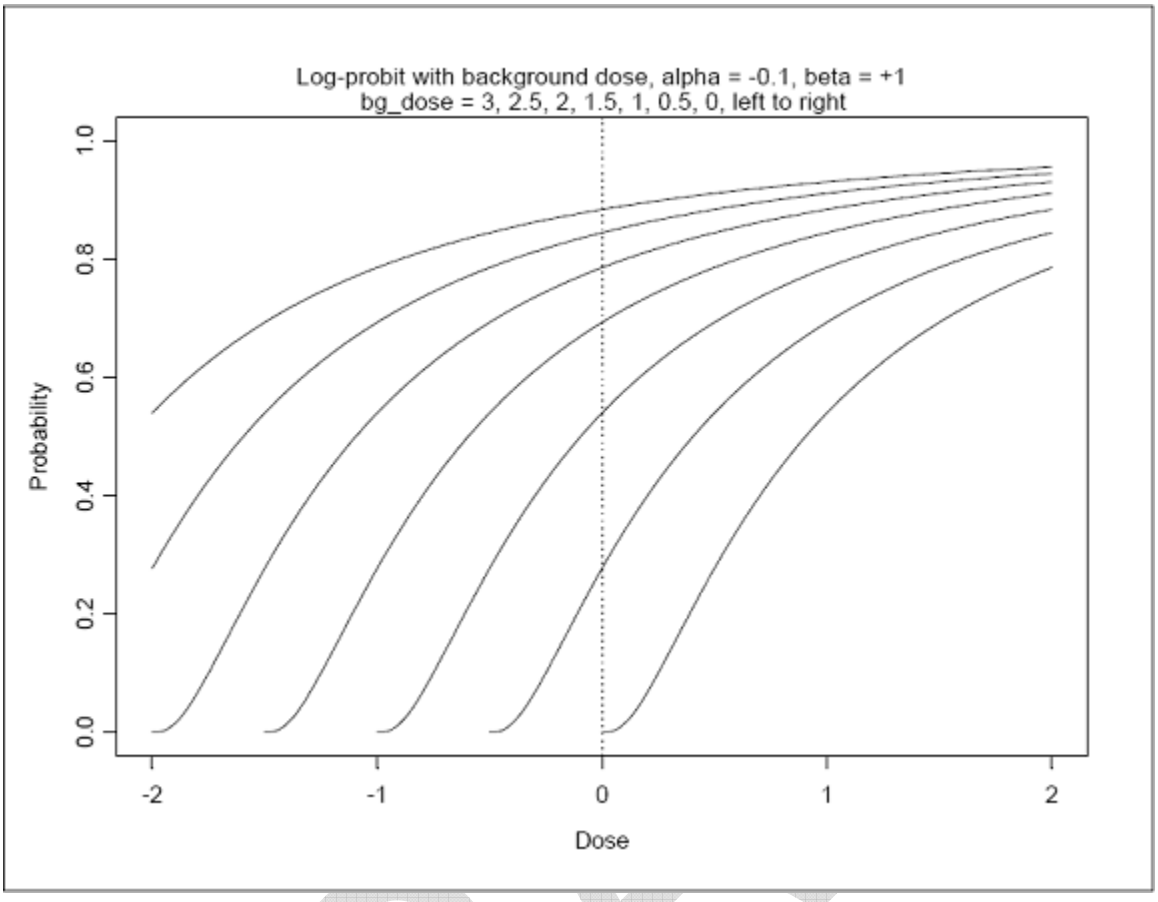


Figure 3 shows an example of fitting an artificial dataset generated using a known log-probit function. In this case, the two log-probit models fit equally well. They differ almost 2-fold in BMDL, and of course one is linear at low doses and the other is sublinear. Figure 4 shows an example of fitting log-probit models to data generated using a log-logistic function, illustrating how the two models, differing in background parameter, will differ in the low-dose region.

Figure 3. Log-probit model with background dose term fitted to data. The model $P = \Phi(\alpha + \beta*(\log(dose + \eta))$, with parameters $\eta = 0.75$, $\alpha = 0.1$, $\beta = 1$, was used to generate probabilities for doses 0, 0.5, 1.0, 1.5, and 2.0. Expected numbers out of 50 animals were rounded to the nearest integer, giving numbers affected of 21, 31, 37, 41, and 43. The model was fitted to these artificial data, yielding estimated parameters $\eta = 0.727918$, $a = 0.108666$, $b = 0.982273$. The solid line shows the exact model used to generate the data, and the dashed line shows the estimated model. Circles show the data as observed proportions of 50 animals affected. Goodness of fit statistics: Chi-square(2) = 0.01, P-value = 0.9929. The log-probit model with background response was also fitted (Chi- square(2) = 0.01, P-value = 0.9942). These models predicted BMDL values of 0.0216005 and 0.0126529, respectively, for extra risk 0.1 at the 95% level.

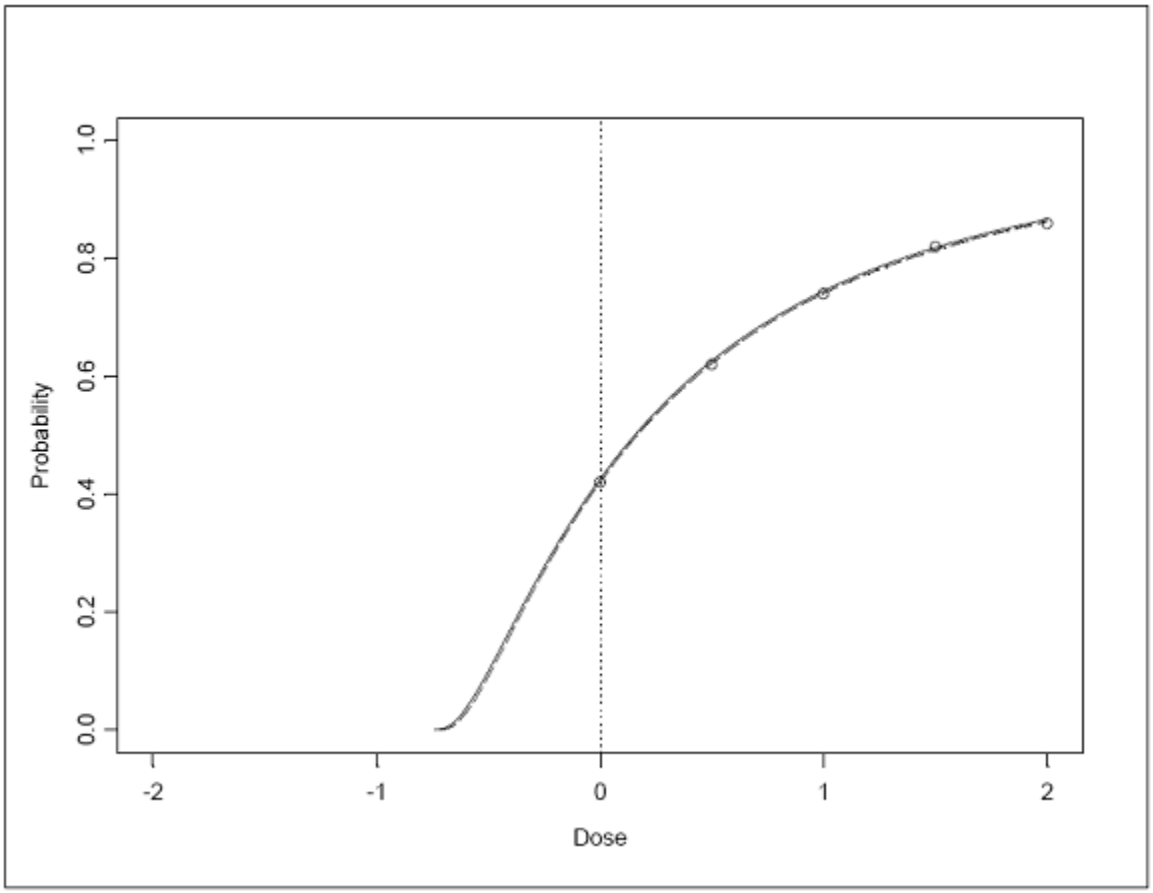
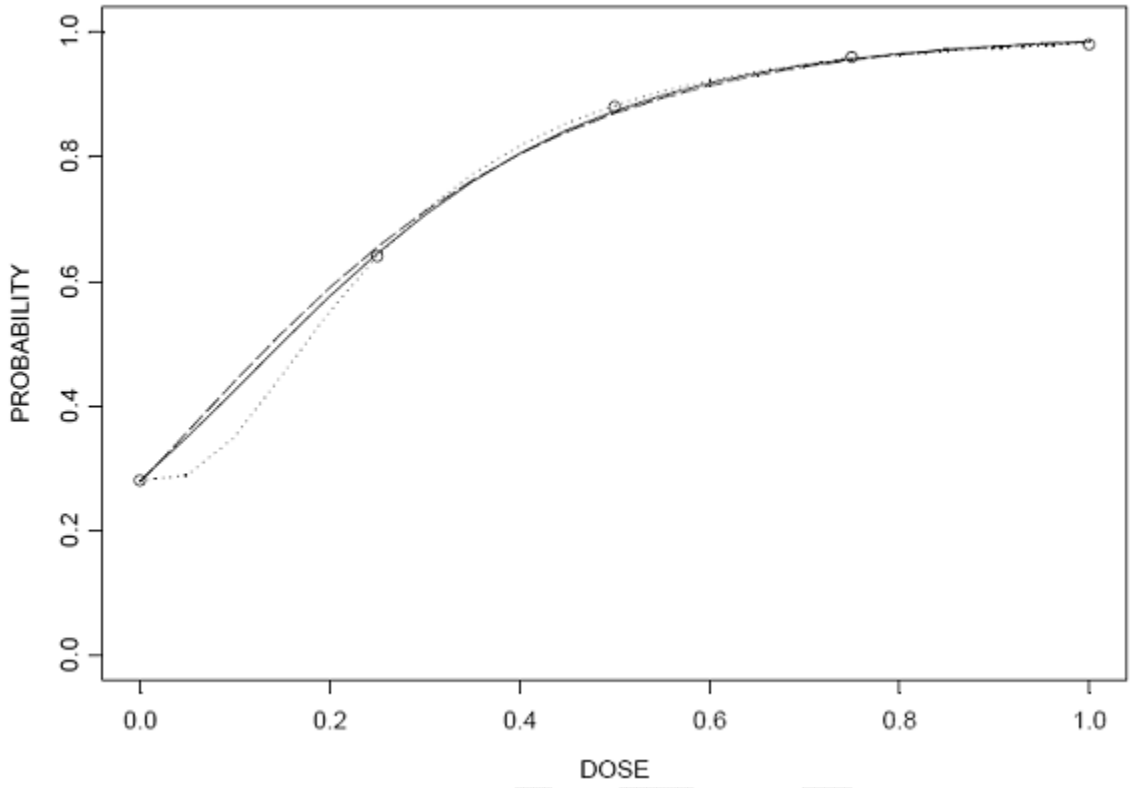


Figure 4. Log-probit model with background dose term fitted to data. The *log-logistic* model P = 1/(-α -β *(log(dose + η)), with parameters η = 1.5, α = -5, β = 10, was used to generate probabilities for doses 0, 0.25, 0.5, 0.75, and 1.0. Expected numbers out of 50 animals were rounded to the nearest integer, giving numbers affected of 14, 32, 44, 48, and 49. The logprobit model with background dose was fitted to these artificial data, yielding estimated parameters η = 0.567585, a = 0.946006, and b = 2.71885. The solid line shows the log-logistic model which generated the data. The dashed line shows the estimated log-probit model with background dose. The dotted line shows the estimated log-probit model with background response. Circles show the data as observed proportions of 50 animals affected. Both log-probit models fit well (Chi-square goodness of fit statistic 0.21 and 0.03, resp.); they estimated BMDs of 0.044 and 0.10, and BMDLs of 0.025 and 0.047, resp.



Application

The primary reason to apply and compare models differing in the background parameter is to better appraise model uncertainty and its implications, including uncertainty about low-dose linearity. Also, for users interested in the maximum likelihood estimate of a response at low doses and its confidence limits, it will be informative to compare these two types of models. Models with and without low-dose linearity can differ greatly in the relative risk predicted at low doses (Krewski and van Ryzin, 1981; NRC, 1980).

Some of the models with a background dose parameter may not fit data well, or may have trouble converging on a solution for the BMD or BMDL, when the observed response at zero dose is large (e.g., 20% to 50% of subjects or more) and the dose-response pattern is unusual (either "flat" or non-monotonic at two or more doses). In other cases, especially when the control response probability is low, the two forms of model may fit a dataset almost equally well. In general, then, users are advised always to review the AIC and goodness-of-fit statistics (including the goodness-of-fit residuals) and to examine plots of the fitted model and data, before deciding whether any model, including a background dose model, fits the data adequately.

Model Fitting and Model Selection Issues

Some of the models with background dose parameter (gamma, Weibull, and log-probit models) may fail to converge on a BMDL solution in one of two situations: (1) when the response data are not strictly increasing, and (2) when the response at zero dose is positive (esp., when it is large, e.g., over 20%).

When the response is not strictly increasing, most or all models may not fit well, and the following questions need to be considered: (a) is the response lower at a high dose because a competing risk is removing animals before the response can occur? If so, should responses be adjusted to account for this?[6] (b) Is it reasonable to remove the high-dose group and fit a model to the reduced dataset? (c) Is the

[6] Piegorsch, W.W. and A.J. Bailer (1997) *Statistics for Environmental Biology and Toxicology*, London: Chapman & Hall. Gart, J.J., K.C. Chu and R.E. Tarone (1979) Statistical issues in interpretation of chronic bioassay tests for carcinogenicity, J. Natl. Cancer Inst. 62: 957-974. Portier, C.J. and A.J. Bailer (1989) Testing for increased carcinogenivity using a survival-adjusted quantal

response inherently non-monotonic, requiring a different type of model? Advice on these questions is provided in the Benchmark Dose Technical Guidance document (on EPA's website "http://cfpub.epa.gov/ncea/", select Publications).

When the response at zero dose is zero or very small, the models with background dose parameter are expected to produce a BMDL. Most cancers in rodent bioassays have zero or very low incidence in the control group.[7] With such data, models with a background dose parameter provide a useful alternative to those background-response models (i.e., the log-probit, loglogistic, gamma and Weibull quantal models) that can have extreme slopes (zero or infinite) as dose nears zero. However, when the response at zero dose is large, BMDL solutions may fail for some background dose models and parameter standard errors may be unusually large. These are signs of problems with near-non-identifiability of parameters and/or a very 'flat' and difficult-to solve likelihood.[8] These should be taken as warning signs that the model is probably not suitable and that the model estimates should not be relied upon.

A question of model selection could arise in comparing the traditional 2-parameter probit or logistic to the new, 3-parameter, background response versions of these models. That is, the chisquare goodness of fit may be enhanced merely by the addition of a parameter. Two considerations are pertinent. First, if either the chi-square value or the AIC value is substantially smaller for one model, it is to be preferred. Second, if the model versions differ only slightly in this respect, the generally accepted practice is to prefer the model with fewer parameters, but if the models predict substantially different BMDLs, it seems best to acknowledge the uncertainty about the true model and its BMDL. It is possible to fit a 2-parameter version of the new background response logistic and probit models by specifying that the intercept parameter be set to zero. However, this is appropriate only when the data are consistent with a response probability of 0.5 or greater for the control (because $F\{\alpha=0,\beta\} \geq 0.5$ for dose ≥ 0). This 2-parameter model could be compared to the traditional logistic or probit model with 2 parameters, and the new background response model with 3 parameters.

Interpretation

In some cases, similar models differing only in the type of background parameter (dose vs. response) may fit data almost equally well; even when they do not, there is no way to infer from mere curve-fitting which model is truer to reality. It is possible to invent even more models that might fit the data adequately but could suggest other interpretations.

The motivation for the background dose parameter was to represent an external dose or internal process acting additively to the applied dose. The background dose parameter may, but does not necessarily, represent a background exposure to the chemical applied in a bioassay or its metabolites (e.g., possible exposure from food, water or air in addition to the experimental exposure). It could also represent the outcome of biological processes generating natural metabolites that act by the same mechanism or that interfere with natural mechanisms which inhibit the mechanism; still more hypotheses could be adduced. Thus, the background dose parameter should not be interpreted literally as support for a particular mechanism unless there is independent evidence to support the particular mechanistic interpretation. Nevertheless, it seems natural to evaluate the fit of background dose models when there is independent evidence about pre-existing or ongoing background exposure.

The background response parameter usually provides a close fit to the response of control animals if the

response test, Fund. Appl. Toxicol. 12: 731-737. Bailer, A.J. and C.J. Portier (1988) An illustration of dangers of ignoring survival differences in carcinogenic data, J. Appl. Toxicol. 8: 185-189. Kodell, R.L., D.W. Gaylor and J.J. Chen (1986) Standardized tumor rates for chronic bioassays, Biometrics 42: 867-873.

[7] Portier, C.J., J.C. Hedges and D.G. Hoel (1986) Age-specific models of mortality and tumor onset for historical control animals in the National Toxicology Program's carcinogenicity experiments, *Cancer Research.* 46: 4372-4378. Gaylor, D.W. (1992) Relationship between the shape of dose-response curves and background tumor rates. Reg. Toxicol. Pharmacol. 16: 2-9.

[8] One useful (but not infallible) diagnostic is to plot a suitable transformation of the empirical probabilities (p = y/n) against the dose metric. If the pattern can be fit well by a linear function, then problems with near-nonidentifiability (Seber and Wild 1989) may be anticipated when fitting the corresponding model with background dose. Transformations: for the log-probit or log-logistic model with background dose, the probits or logits of p; for the Weibull model with background dose, log(-log(1-p)).

overall model fit is good. As with the background dose parameter, one should beware of too literal an interpretation. The model could be interpreted literally to mean that a proportion γ of animals will have cancers of 'natural' origin at every dose and that a proportion (1-γ) F(dose; β) of animals will have cancers attributable to the carcinogen. This clearly goes beyond the data and its support would require experiments especially designed to test this interpretation.

3.4 Dichotomous Hill Model Description

Model Form
The form of the probability function for the Dichotomous Hill model is:

Prob{response} = v*g +(v-v*g)/[1+Exp(-a-b*Ln(dose))]

When d = 0, Prob{response} = v * g.

Parameters

- "v" is the maximum probability of response predicted by the model ($0 < v \leq 1$)
- "g" multiplied by v (v*g) is the background estimate of the probability of response
- "intercept" is a
- "slope" is b

Special Options

Restrict Slope ≥ 1: if the slope is allowed to be less than 1, the slope of the dose-response curve is infinite at zero dose.

BMD Computation

The BMD estimate for the Dichotomous Hill model is defined by the following equation.

Added risk:

$$BMD = e^{\frac{-a - Log\left[-\frac{BMR - v + g * v}{BM}\right]}{b}}$$

Extra risk:

$$BMD = e^{\frac{-a - Log\left[-\frac{BMR - v + g * v - BMR * g * v}{BMR(-1 + g * v)}\right]}{b}}$$

BMDL Computation

To calculate the BMDL, the defining equations for the BMD are solved for the intercept parameter which is then replaced in the original model equations. This makes *BMD* appear in the model equations as a parameter. See BMDL Computation in Dichotomous Model Description: for further details.

3.5 Nested Model Descriptions

Special Considerations for Models for Nested Dichotomous Endpoints

The most common application of the models in this section will be to developmental toxicology studies of organisms that have multiple offspring per litter, as do rodents. In these study designs, pregnant females ("dams") are given one or several doses of a toxicant, and the fetuses, embryos, or term offspring ("pups") are examined for signs of abnormal development. In such studies, it is usual for the responses of pups in the same litter to be more similar to each other than to the responses of pups in different litters ("intra-litter correlation", or "litter-effect"). Another way to describe the same phenomenon is that the variance among the proportion of pups affected in litters is greater than would be expected if the pups were responding completely independently of each other.

The models in this section make available two approaches to this feature of developmental toxicology studies: they use a probability model that provides for extra inter-litter variance of the proportion of pups affected (the beta-binomial probability model: see "Likelihood Function"); and they incorporate a litter-specific covariate that is expected to account for at least some of the extra inter-litter variance. This latter approach was introduced by Rai and Van Ryzin (1985), who reasoned that a covariate that took into account the condition of the dam *before* dosing might explain much of the observed litter effect. Those authors suggested that litter size would be an appropriate covariate. For the reasoning to apply strictly, the measure of litter size should not be affected by treatment; thus, in a study in which dosing begins after implantation, the number of implantation sites would seem to be an appropriate measure. On the other hand, the number of live fetuses in the litter at term would not be an appropriate measure if there is any prenatal death or resorption (this has apparently been ignored in most of the literature).

Carr and Portier (1991), in a simulation study, warn that in situations in which there is no effect of litter size, statistical models that incorporate a litter size parameter, as do the models in BMDS, will often erroneously indicate that there is a litter size effect. Thus, the user should use litter size parameters with caution. Unfortunately, there are currently no good diagnostics for determining whether a litter size effect actually exists.

Likelihood Function

Let ***g*** represent the number of dose groups. For the ***ith*** group, there are n_i pregnant females administered dose $dose_i$. In the ***jth*** litter of the ***ith*** dose group there are s_{ij} ***fetuses***, x_{ij} affected fetuses, and, potentially, a litter-specific covariate r_{ij} which will often be a measure of potential litter size, such as number of implantation sites, though this is not a requirement of the models. In what follows, the dose-response model, which gives the probability that a fetus in the ***jth*** litter of the ***ith*** dose group will be affected is represented by

$$p(dose_i, r_{ij})$$

The beta-binomial distribution can be thought of as resulting from sampling in two stages. First, each litter is assigned a probability, P_{ij} from a beta distribution (beta distributions represent a two parameter family of probability distributions defined on the interval (0,1)). The parameters of the beta distribution are determined by the administered dose, the litter specific covariate r_{ij} and the degree of intra-litter correlation, v_i. Note that the intra-litter correlation parameter varies among doses. It is well known (Williams et al., 1988) that when the true intra-litter correlation differs among doses, unbiased estimates of the other parameters in a dose-response model can only be obtained if dose-specific intra-litter correlation parameters are estimated. As a special case, if $v_i = 0$, then this part of the process is completely deterministic, and

$$P_{ij} = p(dose_i, r_{ij})$$

This allows for the possibility of no litter effect at all.

In the second stage of sampling, s_{ij} ***fetuses*** are assigned to the litter, and the number of affected fetuses, x_{ij} is sampled from a binomial distribution with parameters P_{ij} and s_{ij}.

The log-likelihood function that results from this process is:

$$L = \sum_{i=1}^{g} \left\{ \sum_{j=1}^{n_i} \left[\sum_{k=1}^{x_{ij}} \ln(p(dose_i, r_{ij}) + (k-1)\psi_i) + \sum_{k=1}^{s_i j - x_{ij}} \ln(1 - p(dose_i, r_{ij}) + (k-1)\psi_i) - \sum_{k=1}^{s_{ij}} \ln(1 + (k-1)\psi_i) \right] \right\},$$

where

$$\psi_i = \phi_i/(1-\phi_i)$$

and

$$\sum_{a}^{b}(.) = 0$$

if ***a > b*** by convention.

BMD Computation

BMD computation is similar to that for dichotomous models with the added wrinkle that a value for the litter-specific covariate is required. The user has the option of specifying either the control group mean of the covariate, or the overall mean. Probably, the overall mean should be preferred, if the covariate is not expected to be affected by dose. Of course, if the covariate is affected by dose, then it should probably not be used, anyway!

BMDL Computation

BMDS currently only calculates one-sided confidence intervals, in accordance with current BMD practice. The general approach to computing the confidence limit for the BMD (called the BMDL here) is the same for all the models in BMDS, and is based on the asymptotic distribution of the likelihood ratio (Crump and Howe, 1985).

The approach used for all the nested dichotomous models is the same. The equations that define the benchmark response in terms of the benchmark dose and the dose-response model are solved for one of the model parameters, using either the control group mean or the overall mean of the litter-specific covariate. The resulting expression is substituted back into the model equations, with the effect of reparameterizing the model so that BMD appears explicitly as a parameter. A value for BMD is then found such that, when the remaining parameters are varied to maximize the likelihood, the resulting log-likelihood is less than that at the maximum likelihood estimates by exactly

$\chi^2_{1,1-2\alpha}/2$

3.5.1 Logistic Nested Model Description

Model Form
The Nested Logistic Model is the log-logistic model, modified to include a litter-specific covariate. The model form for the Nested Logistic Model is:

Prob{response} = $\alpha+\theta_1 r_{ij} + (1 - \alpha - \theta_1 r_{ij}) / (1 + \exp[-\beta-\theta_2 r_{ij} - \rho*\text{Ln}(\text{dose})])$

if ***dose*** **> 0**, and **α** + **$\theta_1 r_{ij}$** if ***dose*** = **0.**

In the above equation r_{ij} is the litter-specific covariate for the ***jth*** litter in the ***ith*** dose group; **α >= 0**, **β >= 0**, **ρ >= 0** with an option to restrict **ρ >= 1**; and $\alpha+\theta_1 r_{ij} \geq 0$ for every r_{ij}.

In addition there are g intra-litter correlation coefficients, $0 < \Phi_i < 1$ (i = 1, ..., g).

Parameters

Intercept	= α
Power	= ρ
Slope	= β
First coefficient for litter-specific covariate	= θ_1
Second coefficient for liter-specific covaritate	= θ_2
Intralitter correlation coefficients	= $\Phi_1 \ldots \Phi_g$

Special Options

Restriction
Power parameter (Rho) can be restricted to be $\geq$ 1 (Default)

Risk Type
Choices are "Extra" or "Added." Additional risk is the additional proportion of total animals that respond in the presence of the dose, or the probability of response at dose d, P(d), minus the probability of response in the absence of exposure, P(0). Extra risk is the additional risk divided by the proportion of animals that will not respond in the absence of exposure, 1 - P(0). Thus, extra and additional risk are equal when background rate is zero.

BMD Computation
If r_m represents either the control mean value for the litter-specific covariate or the overall mean, then the BMD is computed as:

BMD = $\text{Exp}\{[\ln(A/(1-A)) - \beta - \theta_2 r_m] / \rho\}$

where

A	=	BMRF	for extra risk
	=	$\text{BMRF}/(1 - \alpha - \theta_1 r_m)$	for added risk

BMDL Computation
The parameter **β** is replaced with an expression derived from the BMD definition (above) in the dose-response function, with the effect of reparameterizing the model so that BMD appears explicitly as a

parameter. A value for BMD is then found such that, when the remaining parameters are varied to maximize the likelihood, the resulting log-likelihood is less than that at the maximum likelihood estimates by exactly

$$\chi^2_{1,1-2\alpha}/2$$

3.5.2 NCTR Model Description

Model Form

The NCTR model is a Weibull model modified to include a litter-specific covariate. The model form is:

Prob{response} = $1 - \text{Exp}\{-(\alpha + \theta_1(r_{ij} - r_m) - (\beta + \theta_2(r_{ij} - r_m) \bullet \text{dose}^{\rho}\}$

where r_{ij} is the litter-specific covariate for the ***jth*** litter in the ***ith*** dose group, r_m is the overall mean for the litter-specific covariate, **α >= 0**, **β >= 0**, **ρ >= 1** with an option to restrict **ρ >= 1**, and

$\theta_1(r_{ij} - r_m) \geq 0$ and $\theta_2(r_{ij} - r_m) \geq 0$

for every r_{ij}.

In addition there are g intra-litter correlation coefficients, **0 < Φ*i* < 1.**

Parameters

Intercept	= α
Power	= ρ
Slope	= β
First coefficient for litter-specific covariate	= θ_1
Second coefficient for litter-specific covariate	= θ_2
Intralitter correlation coefficients	= $\Phi_1 \ldots \Phi_g$

Special Options

Restriction
Power parameter **ρ (Rho)** can be restricted to be ≥ 1 (Default)

Risk Type
Choices are "Extra" or "Added." Additional risk is the additional proportion of total animals that respond in the presence of the dose, or the probability of response at dose d, P(d), minus the probability of response in the absence of exposure, P(0). Extra risk is the additional risk divided by the proportion of animals that will not respond in the absence of exposure, 1 - P(0). Thus, extra and additional risk are equal when background rate is zero.

BMD Computation

BMD = $[-(\text{Ln}(1-A)) / (\beta + \theta_2\delta_r)]^{(1/\rho)}$

where δ_r is the average of $(r_{ij} - r_m)$ over either the control group or over all observations, depending upon the option selected for "Fixed Litter Size" (when using the overall mean, δ_r is always 0), and

A	=	BMRF	for extra risk
	=	BMRF/$(1-\alpha-\theta_1\delta_r)$	for added risk

BMDL Computation

The parameter **β** is replaced with an expression derived from the BMD definition (above) in the dose-response function, with the effect of reparameterizing the model so that BMD appears explicitly as a parameter. A value for BMD is then found such that, when the remaining parameters are varied to maximize the likelihood, the resulting log-likelihood is less than that at the maximum likelihood estimates by exactly

$$\chi^2_{1,1-2\alpha}/2$$

3.5.3 Rai and Van Ryzin Model Description

Model Form

The Rai and Van Ryzin model is a Weibull model modified to include a litter-specific covariate. The model form is:

Prob{response} = $[1 - \text{Exp}\{-\alpha-\beta\bullet\text{dose}^{\rho}\}] \bullet \text{Exp}\{-(\theta_1 + \theta_2\text{dose})\bullet r_{ij}\}$

where r_{ij} is the litter-specific covariate for the ***jth*** litter in the ***ith*** dose group, **α >= 0**, **β >= 0**, **θ >= 0** with an option to restrict **θ >= 1**, and

$(\theta_1 + \theta_2\text{dose}_i) > 0$, for all doses (i = 1, ..., g).

In addition there are g intra-litter correlation coefficients, **$0 < \Phi i < 1$.**

This is a generalization of the model described in Rai and Van Ryzin (1985) by the addition of the power parameter, **ρ**. To get the conventional Rai and Van Ryzin model, fix the power parameter to 1.

Parameters

Intercept	= α
Power	= ρ
Slope	= β
First coefficient of litter-specific covariate	$= \theta_1$
Second coefficient of litter-specific covariate	$=\theta_2$
Intralitter correlation coefficients	$= \Phi_1 \ldots \Phi_g$

Special Options

Restriction
Power parameter **ρ (Rho)** can be restricted to be ≥ 1 (Default)

Risk Type
Choices are "Extra" or "Added." Additional risk is the additional proportion of total animals that respond in the presence of the dose, or the probability of response at dose d, P(d), minus the probability of response in the absence of exposure, P(0). Extra risk is the additional risk divided by the proportion of animals that will not respond in the absence of exposure, 1 - P(0). Thus, extra and additional risk are equal when background rate is zero.

BMD Computation
The BMR formulas are solved numerically for the BMD.

BMDL Computation
The parameter **β** is replaced with an expression derived from the BMD definition in the dose-response function, with the effect of reparameterizing the model so that BMD appears explicitly as a parameter. A value for BMD is then found such that, when the remaining parameters are varied to maximize the

likelihood, the resulting log-likelihood is less than that at the maximum likelihood estimates by exactly.

3.6 Toxicodiffusion Model Description

Model Form

The Toxicodiffusion model has the following form for describing the time course of responses before and after an exposure to a dose:

$$\eta(d,t) = A(t) + B \cdot t \cdot d \cdot \exp(-k \cdot t)/(1 + C \cdot d \cdot t \cdot \exp(-k \cdot t))$$

where

$A(t) = A_0$ or
$A(t) = A_0 + A_1 t$ or
$A(t) = A_0 \_ A_1 t + A_2 t^2$

depending on the "background degree" specified by the user. A(t) applies before exposure and for all times in the absence of exposure (or to "sham" exposures to dose=0). Thus the Toxicodiffusion model is applicable to data with the following characteristics:

- An outcome (response variable) measured on a continuous scale.
- Single exposure (or exposure interval), to several (4-5 recommended) "dose" levels.
- Duration of the experiment (the time component) coded between 0 and a maximum positive value, with 0 being the beginning and the maximum positive value the last time point at which data are available. The time at which exposure took place must be known and coded by a value between 0 and the maximum value.
- The outcome is observed (and recorded) repeatedly over time on each study subject; the timing of the observation is given. It is not required, however, that each subject (experimental unit) yield an equal number of observations at the same time points.
- Observations should not be aggregated over subject, and data must be identifiable with each subject.
- Multiple subjects per dose group.
- Dose effects are preferably observed at more than one dose level.
- Differences in dose effects are seen at some time points.

The model fitting is accomplished by maximizing the likelihood of the data, assuming a random effects model for the parameter A_0 (normally distributed across individuals) and a normal error distribution (observations are normally distributed around the model-predicted individual-, dose-, and time-specific means).

Parameters

Background parameters = A_0, A_1, A_2

Time-course parameters = B, C, k

Special Options

None

Risk Type

Risk is defined in terms of added or extra risk. Because the Toxicodiffusion model is for continuous responses, this requires specification of response levels that are considered adverse. That is done in one of two ways. First, the assumed background rate (probability) of adverse response may be specified; in that case the cut-off(s) that yield that probability of response are determined from the fit of the model.

Second, the cut-off value(s) may be specified directly; that yields an estimated background rate of response once the model is fit. In either case, the extra or added risk is calculated for any dose (and time) based on the model-predicted increase in the proportion of responses beyond the cut-off(s).

BMD Computation

The BMD output from a Toxicodiffusion model run is the lowest dose for which, at some time after exposure, the extra or added risk is equal to the BMR Risk Level specified by the user. Note that because the response rates vary over time, there will be several dose levels that yield the BMR response at various time points. The minimum of those doses is the reported minimum BMD.

BMDL Computation

The BMDL is estimated via bootstrap resampling of residuals and random effects. The residuals and random effects are estimated from the original fitting of the model. They are resampled (within or across dose groups) treating the vector of residuals for an individual as the sampling unit if need be. BMDs are calculated as discussed above for each set of bootstrapped observations. The percentiles over all the bootstrapped BMDs are used to define confidence bounds for the BMD (e.g., the 5^{th} percentile would be reported as the 95% lower bound on the BMD).

3.7 Conc_x_Time Model Description

Model Form

The only concentration-time model currently in BMDS 2.1 is the ten Berge model which has the following form:

Prob{response} = h(z)
where h() is either the logit or the probit function

$h(z) = \exp(z) / (1 + \exp(z))$ for Logit link function
$= \Phi(z-5)$ for Probit link function.

and $\Phi()$ is the standard normal cumulative distribution function. The variable z is a linear function of the terms in the model as follows:

$$z = B_0 + B_1*f_C(C) + B_2*f_T(T) + B_3*f_x(x) + B_4*r_4(C, T, x) + B_5*r_5(C, T, x) + \ldots$$

where $f_i(u)$ = transformation of concentration (i=C), time (i=T), or covariate (i=x);
$r_j(C, T, x)$ = interactions (products) of the $f_C(C)$, $f_T(T)$, and $f_x(x)$ terms.

The f_i transformations that have been implemented include:

$f_i(u)$ =	Transformation
u	Identity
ln(u)	Logarithmic
1/u	Reciprocal

Note that the covariable "x" is actually a place holder for any number of possible explanatory variables of interest (think of x as a vector of variables above and beyond the C and T variables).

Parameters

Intercept = B_0
Coefficients of the model terms = $B_1, \ldots, B_n$

(currently the BMDS version of the model allows up to five main effects variables and three product terms, so that n is less than or equal to 8).

Special Options

None

Risk Type
There are no specific risk type choices. The model calculates a concentration (or the value of any other variable) given the values of the other variables in the model such that the *probability* of response is equal to some specified value. If the background probability is 0, as it would be if the logarithmic transformation is used for all the explanatory variables in the model, then the probability of response for a set of values for the model variables is equal to the added or extra risk for that set of values.

BMD Computation
The BMD (concentration yielding a specific probability of response, given the values of the other model variables) is computed numerically from the set of MLE parameter values.

BMDL Computation
A Wald-type confidence interval is determined for all model parameters (including the "BMD" as defined above). The confidence bounds determined in this manner for the BMD yield the BMDU and BMDU. The user must specift a deviate value corresponding to the confidence level of interest; this deviate can be determined from the standard normal distribution or, perhaps more appropriately, from a T distribution with degrees of freedom determined from the number of observations and the number of fitted parameters.
Note about model graphics: because the graphical representation of the ten Berge modeling results is quite different from that obtained from other BMDS models, the currentl version of BMDS does not include a graphical output for the ten Berge model. Users desiring plots of contours of response probabilities on the Concentration-Time plane should consider porting the modeling results to Excel and creation of plots using that software.

4 TEXT OUTPUT FROM MODELS

The purpose of the BMDS output pages is to provide the user with goodness-of-fit criteria and model results to aid in determining the appropriateness of the subject model to the benchmark dose derivation. While BMDS will estimate parameters etc. for the user, it is the users responsibility to interpret these results before making use of the BMDL. The BMDS model text output also provides information relevant to whether or not the function maximization problem was actually accomplished. That is, for each model, parameters are estimated using Maximum Likelihood procedures through an iterative routine. There is no guarantee that the model parameters will in fact achieve the true maximization, and by inspecting the output pages, the user should be able to obtain at least some idea as to whether or not it was achieved. While all models tend to follow a similar format, there are some differences in the output pages given by certain models.

The output pages also give the user a quick verification of the options they had selected on the model run screen. For instance, when two users may be comparing results and obtained different answers, they may consult the output pages to make sure the settings were the same or if they had used the same (or most current) version of the software/models.

4.1 Continuous Model Text Output

The continuous output page starts with a few explanatory lines that the user can reference quickly to: check the version number, the date and time of run, the input data set used, verify that all the correct options were set, check which model was used, see the explicit form of the mean function for the model run, and get some basic data summaries (number of dose levels, etc). The output page is designed so

that it will provide a reliable basis for reentering BMDS and accurately reproducing the results of a run (e.g., with an updated model) at a later date. The "form of the response function" is provided on each model's text output page, and is the model function that BMDS will estimate parameters for in order to derive the Benchmark Dose.

Default Initial Parameters:

These are computer generated values that provide the starting point for the iterative maximization routine used by BMDS. This may give the user a basis for appropriate parameter values should they want to rerun the program if a maximum wasn't found, not believable, etc.

Parameter Estimates:

The parameter estimates are the actual estimates the program routine has found for the particular model run. This table includes both the estimates for the true parameter values as well as their estimated standard errors. The standard errors are given for two reasons: (1) If standard errors are extraordinarily high, then the user should suspect that the probability function may not have reached a maximum, and they may want to use different starting points. There is not a guarantee if these are high that the function has not, in fact, been maximized. The user should use this in conjunction with other output to make a decision. (2) To make inferences about the population parameters themselves. Under certain assumptions, the user maybe able to formulate tests for the true value of the parameter.

Asymptotic Correlation Matrix of Parameter Estimates

This table provides the user with a matrix of correlation estimates between each of the parameters. Again, if these values seem to be high (in this case, very close to 1), there may have been a problem in the maximization. However, as stated before, high correlation does not confirm that the problem of maximization in fact failed.

Table of Data and Estimated Values of Interest

This table gives a listing of the data as well as estimated means and standard deviations from the model. This is a good place for the user to look, along with the Tests of Fit and Maximum Likelihood below, to judge the appropriateness of the model. If a model fits well, the observed and estimated means should be relatively close. The scaled residual values printed at the end of the table are defined as follows:

(Obs. Mean - Predicted Mean)/SE,

where the Predicted Mean is from the model and SE equals the estimated standard deviation (square root of the estimated variance) divided by the square root of the sample size.

The overall model should be called into question if the scaled residual value for any individual dose group, particularly a low dose group, is greater than 2 or less than -2.

Tests of Fit and Maximum Likelihood

Continuous Model Maximum Likelihood Help

The BMDS uses likelihood theory to estimate function parameters and ultimately to make inferences about risk assessment data. Maximum likelihood is the process of estimating the models parameters such that a likelihood function is maximized according to the data. In other words, parameter values are "chosen" such that the subject model (i.e. polynomial or power) obtains the best possible fit to the data, given the constraints of the model's parameter structure. For example, suppose one wishes to fit a second degree polynomial model with a constant variance to a data set. The particular form of this model would be:

$Y = b0 + b1 * X + b2 * X^2$

The parameters we wish to estimate in this case would be b0, b1, and b2, as well as the constant variance parameter, call it Sigma^2. To estimate these parameters, BMDS uses maximum likelihood procedures. The end result being a vector of parameters that maximizes the likelihood function for the model specified. The "Log(likelihood)" value given on the BMDS output page is the maximum value of the natural logarithm of the likelihood function. Also note that there are an associated number of degrees of

freedom at each likelihood calculated. The degrees of freedom in each case is the number of parameters estimated in that particular model. In the example above, 4 parameters were estimated, and thus, this likelihood has 4 degrees of freedom.

The Akaike's Information Criterion (AIC) (Akaike, 1973; Linhart and Zucchini, 1986; Stone, 1998) value given on the BMDS output page is $-2L + 2p$, where L is the log-likelihood at the maximum likelihood estimates for the parameters, and p is the number of model parameters estimated. It can be used to compare different types of models which use a similar fitting method, as do all dichotomous, continuous and nested model types within BMDS. The model with the lowest AIC would be presumed to be the better model under this method. Although such methods are not exact, they can provide useful guidance in model selection.

The BMDS output page gives four or five likelihood (and AIC) values, depending on the variance model chosen, that may be of interest to the user. These values are later used in asymptotic Chi-Square **tests of fit.** Each of these likelihood values represents a model a user may consider in the analysis of the data. The five models are:

"Full-constant variance" Model -	A1:Yij = Mu(i) + e(ij), Var{e(ij)} = Sigma^2
"Fullest" Model -	A2:Yij = Mu(i) + e(ij), Var{e(ij)} = Sigma(i)^2
"Full-modeled variance" Model -	A3:Yij = Mu(i) + e(ij), Var{e(ij)} = alpha*(Mu(i))^rho
"Reduced" Model -	R: Yi = Mu + e(i), Var{e(i)} = Sigma^2

Fitted Model: The user specified model.

Model A1 would be a "full" model that fits all the means at the user specified dose levels. This model also implies a constant variance at each dose level. This likelihood may be of interest in order to determine whether or not a constant variance model adequately describes the data. Model A2 would be the "fullest" model. It would describe a data set that has an individually estimated mean at each dose level, as well as a non-constant variance that does not have any functional relationship to the mean. Model A3 is similar to model A2, and only differs in its variance parameters. In this case, the model is considered to have a non-constant variance over the dose levels, but this variance is modeled as a function of the mean. The reduced model is the model that implies no real difference in mean or variance over the dose levels. In other words, if this model is deemed adequate to describe the data, risk assessment may not be appropriate, as there is no adverse effects over the dose levels considered (i.e., the mean and variance do not fluctuate). The last model, the fitted model, is the user specified model. A user may have reason to believe that a certain model may describe the data well, and thus uses it to make inferences about the population in order to calculate the BMD and BMDL.

Tests of Fit

The BMDS software provides three or four different Tests of Fit that the user may use to determine an appropriate model for fitting their data. These Tests of Fit are based on asymptotic theories of the likelihood ratio. Without getting too technical, the likelihood ratio is just the ratio of two **likelihood** values, many of which or given in the BMDS output. Statistical theory proves that -2*log(likelihood ratio) converges to a Chi-Square random variable as the sample size gets large and the number of dose levels gets large. These values can in turn be used to obtain approximate probabilities to make decisions about model fit. Chi-Square tables can be found in almost any statistical book.

Each of the four/five models, described in Help under **likelihood**, has a likelihood value. The BMDS program uses these values to create ratios from two models that form a meaningful test. Suppose the user wishes to test two models for fit, A and B. One assumption that is made for these tests is that the "true" model is in fact B, but it can be simplified in such a way that the simplified model describes the data as well as B. Also suppose A is a much simpler model in that it has much fewer parameter values (the goal is to simplify the model as much as possible without losing information about the data). Assume each model has a maximum likelihood value, call them L(A) and L(B). A ratio can be formulated easily: L(A)/L(B) (Note: The model with a higher number of parameters is always in the denominator of this ratio). Now, using the theory, -2*log{ L(A)/L(B)} approaches a Chi-Square random variable. This can be simplified by using the fact that the log of a ratio is equal to the difference of the logs, or simply put, -

2*log{ L(A)/L(B)} = -2*(log{L(A)} - log{L(B)}) = 2*log{L(B)} - 2*log{L(A)}. The likelihood values given by BMDS are in fact the log likelihoods, so this becomes just a subtraction problem. This value can then in turn be compared to a Chi-Square random variable with a specified number of degrees of freedom.

As mentioned on the **Likelihood** Help screen, each log likelihood value has an associated number of degrees of freedom. The number of degrees of freedom for the Chi-Square test statistic is merely the difference between the two model degrees of freedom. In the mini-example above, suppose L(A) has 5 degrees of freedom, and that L(B) has 8. In this case, the Chi-Square value you would compare this to would be a Chi-Square with 8 - 5 = 3 degrees of freedom.

In the A vs B example, what is exactly being tested? In terms of hypotheses, it would be:

H0: A models the data as well as B

H1: B models the data better than A

Keeping these tests in mind, suppose 2*log{L(B)} - 2*log{L(A)} = 4.89 based on 3 degrees of freedom. Also, suppose the rejection criteria is a Chi-Square probability of less than .05. Looking on a Chi-Square table, 4.89 has a p-value somewhere between .10 and .25. In this case, H0 would not be rejected, and it would seem to be appropriate to model the data using Model A.

The BMDS software provides three or four default tests, depending on the variance model the user has specified (constant variance model, or a non-constant variance model where the variance is a function of the mean, namely, Sigma(i)^2 = alpha*(Mu(i))^rho). BMDS assumes rejection criteria is a Chi-Square probability of less than .05 for all of the tests, however p values are presented so that the user is free to use any rejection criteria they want. Each test in each model will be discussed in some detail below.

Test 1 (A2 vs R): Tests the hypothesis that response and variance don't differ among dose levels. If this test accepts, there may not be a dose-response.

Using Model A2 and model R, a likelihood ratio is formulated to determine whether the data vary at all among dose groups. If this test accepts, then there may not be a dose-response, although it is probably possible for some data sets with a slightly significant trend to not reject this test. This model implies no differences in the mean, nor in the variance at each dose level, and thus, there would be no adverse effect as dosage is increased. If this test rejects, then modeling the data is appropriate, and the user should consider the tests below.

Test 2 (A1 vs A2): Tests the hypothesis that variances are homogeneous. If this test accepts, the simpler constant variance model may be appropriate.

Recall that the goal is to simplify the model. If this test accepts, it may be appropriate to go with the simpler constant variance model. If this test rejects, the user may want to run a non-constant variance model, or if the non-constant variance model was run, then the user should look at the second test 3 below to make further decisions.

Test 3 (Test 4 in non-constant variance model) (Fitted vs A3): Tests the hypothesis that the model for the mean fits the data. If this tests accepts, the user has support for the selected model.

This test is used to give some indication as to whether or not the user specified model is appropriate to model data. On the BMDS user screens, the user specifies a model that they may believe is the true, or near true, model. If this test accepts, the user has support for the choice of model, and may deem it adequate for data modeling. If this test rejects, the user may want to try a different model.

Test 3 (Non-constant variance model) (A3 vs A2): Test the hypothesis that the variances are adequately modeled. If this test accepts, it may be appropriate to conclude that the variances have been modeled appropriately.

Here, the test is one to see whether or not the variance model, Sigma(i)^2 = alpha*(Mu(i))^rho, is an appropriate assumption. Again, the purpose is to reduce the parameter space, and by modeling the variances as a function of the mean (which also intuitively makes sense that variance may have some dependence on the mean value) we achieve some reduction. If this tests accepts, it may be appropriate to conclude that the true variances have the form above. If this test rejects, unfortunately BMDS has no further way to model variance. Look for different variance models in future releases of BMDS.

4.2 Dichotomous Model Text Output

The dichotomous output page starts with a few explanatory lines that the user can reference quickly to: check the version number, the date and time of run, the input data set used, check which model was used, see the explicit form of the response function, verify that all the correct options were set and get some basic data summaries (number of dose levels, etc). The output page is designed so that it will provide a reliable basis for reentering BMDS and accurately reproducing the results of a run (e.g., with an updated model) at a later date. The "form of the response function" is provided on each model's text output page, and is the model function that BMDS will estimate parameters for in order to derive the Benchmark Dose.

Default Initial Parameters:

These are computer generated values that provide the starting point for the iterative maximization routine used by BMDS. This may give the user a basis for appropriate parameter values should they want to rerun the program if a maximum wasn't found, they just don't believe the answer, etc.

Parameter Estimates:

The parameter estimates are the actual estimates the program routine has found for the particular model run. This table includes both the estimates for the true parameter values as well as their estimated standard errors. The standard errors are given for two reasons: (1) If standard errors are extraordinarily high, then the user should suspect that the probability function may not have reached a maximum, and they may want to use different starting points. There is not a guarantee if these are high that the function has not, in fact, been maximized. The user should use this in conjunction with other output to make a decision. (2) To make inferences about the population parameters themselves. Under certain assumptions, the user maybe able to formulate tests for the true value of the parameter.

Asymptotic Correlation Matrix of Parameter Estimates

This table provides the user with a matrix of correlation estimates between each of the parameters. Again, if these values seem to be high (in this case, very close to 1), there may have been a problem in the maximization. Also, as stated before, high correlation does not confirm that the problem of maximization in fact failed. The Weibull model, for instance, tends to give high correlation between the slope and power parameters, even when the likelihood was maximized.

Analysis of Deviance Table

The analysis of deviance table lists three maximum likelihood values. The first is the "full model". The full model would be any model that would perfectly fit all the positive response proportions at the dose levels specified by the user. The second model is the "fitted model" maximum likelihood value. This is the value of the maximum likelihood function for the particular model selected and using the estimated parameter values. The last likelihood value is the "reduced model" value, which would be the value of the likelihood function if all data points where assumed to come from the same population with the same population parameter. That is, for each dose level, the actual probability of an adverse effect would be the same. These values are just the likelihood functions evaluated according to the assumptions made at each step (i.e., the model assumption for the fitted model).

Next to the likelihood values there are three values: Deviance, degrees of freedom (DF), and P-value. The Deviance is the difference between the fitted or reduced model and the full model likelihood values. This deviance measures whether or not the smaller model (i.e., the fitted or reduced model) describe the data as well as the full model does. This deviance is then used to formulate a Chi-Square random variable that tests exactly that. The user may choose a rejection level (.05 is common) to test whether or not the model fit is appropriate. The p-value for testing whether or not the fitted model adequately describes the data is given next to the fitted model likelihood, and the user can reject or not reject a hypothesis according to the p-value given . The reduced model p-value would be used in the same way, but here the user would be testing whether or not there is in fact a dose/response relationship where the true population proportion is a function of dose, as opposed to a single population with one parameter (the proportion of affected animals).

It will often happen that several models provide an adequate fit to a given data set. These models may be

essentially unrelated to each other (for example a logistic model and a probit model often do about as well at fitting dichotomous data) or they may be related to each other in the sense that they are members of the same family that differ in which parameters are fixed at some default value. One can consider the log-logistic, the log-logistic with non-zero background, and the log-logistic with threshold and non-zero background to all be members of the same family of models. Generally, within a family of models, as additional parameters are introduced the fit will appear to improve. Goodness-of fit statistics presented in the main body of the Analysis of Deviance Table can be used to compare such related models, but are not designed to compare unrelated models. Alternative approaches are need for selecting between models that are not related (not in the same family).

The Akaike's Information Criterion (AIC; Akaike, 1973; Linhart and Zucchini, 1986; Stone, 1998) is defined as $-2L + 2p$, where L is the log-likelihood at the maximum likelihood estimates for the parameters, and p is the number of model parameters estimated. The AICs for the model run are provided at the bottom of the Analysis of Deviance Table. They can be used to compare different types of models which use a similar fitting method (for example, least squares or a binomial maximum likelihood), as do all dichotomous, continuous and nested model types within BMDS. The model with the lowest AIC would be presumed to be the better model under this method. Although such methods are not exact, they can provide useful guidance in model selection.

Goodness of Fit

This table gives both a listing of the data as well as residual and overall Chi-Square Goodness of Fit tests. This is a good place for the user to look outside of the Analysis of Deviance table to judge the appropriateness of the model. The table lists estimated probabilities, the expected and observed number of affected animals and scaled residuals for each dose group. If a model fits well, the observed and expected number of affected animals should be relatively close. The overall scaled residual value, and it corresponding p-value are indications of that "closeness". If the p-value is larger than some predetermined critical p-value, then the user may be able to conclude that the model is appropriate to model the data. The scaled residual values printed at the end of the table are defined as follows:

(Obs. - Expected)/sd,

where "Expected" is the expected number of responders from the model and sd equals the estimated standard deviation (square root of the estimated variance) of the expected number. For these models, the estimated variance is equal to n*p*(1-p) where n is the sample size and p is the model-predicted probability of response. The overall model should be called into question if the scaled residual value for any dose group, particularly a low dose group, is greater than 2 or less than -2.

Slope at ED(10) - *Cancer Model Only*

Some additional assessment tools are imparted by the draft beta Cancer model at this time. The output page for the draft beta cancer model includes an estimate of the slope of the BMD curve at the ED(10) (the 10 percent extra risk response level) and the two sided 95.0% confidence interval for the slope at the ED(10). The two sided 95.0% confidence interval for the linear term of the model is also provided. Finally, *scaled residuals* are reported to aid in determining how well the model fits the data at low doses.

Benchmark Dose Computation

This is the ultimate goal of the BMDS software (see Overview). The BMD or BMDL is the value that the user will use when determining the RfD or RfC for the particular toxicant being studied. The user should investigate all the output to this point, and then make the decision to accept this as a valid BMDL.

4.3 Nested Model Text Output

The nested model output page starts with a few explanatory lines that the user can reference quickly to: check the version number, the date and time of run, the input data set used, verify that all the correct options were set, check which model was used, see the explicit form of the mean function for the model run, and get some basic data summaries (number of dose levels, etc). The output page is designed so that it will provide a reliable basis for reentering BMDS and accurately reproducing the results of a run

(e.g., with an updated model) at a later date. The "form of the response function" is provided on each model's text output page, and is the model function that BMDS will estimate parameters for in order to derive the Benchmark Dose.

Default Initial Parameters:

These are computer generated values that provide the starting point for the iterative maximization routine used by BMDS. This may give the user a basis for appropriate parameter values should they want to rerun the program if a maximum wasn't found, they just don't believe the answer, etc.

Parameter Estimates:

The parameter estimates are the actual estimates the program routine has found for the particular model run. This table includes both the estimates for the true parameter values as well as their estimated standard errors. The standard errors are given for two reasons: (1) If standard errors are extraordinarily high, then the user should suspect that the probability function may not have reached a maximum, and they may want to use different starting points. There is not a guarantee if these are high that the function has not, in fact, been maximized. The user should use this in conjunction with other output to make a decision. (2) To make inferences about the population parameters themselves. Under certain assumptions, the user maybe able to formulate tests for the true value of the parameter.

Analysis of Deviance Table

The analysis of deviance table list three maximum likelihood values. The first is the "full model". The full model would be any model that would perfectly fit all the positive response proportions at the dose levels specified by the user. The second model is the "fitted model" maximum likelihood value. This is the value of the maximum likelihood function for the particular model selected and using the estimated parameter values. The last likelihood value is the "reduced model" value, which would be the value of the likelihood function if all data points where assumed to come from the same population with the same population parameter. That is, for each dose level, the actual probability of an adverse effect would be the same. These values are just the likelihood functions evaluated according to the assumptions made at each step (i.e., the model assumption for the fitted model).

Next to the likelihood values there are three values: Deviance, degrees of freedom (DF), and P-value. These are asymptotic Chi-Square test that investigate the appropriateness of the model fit, as well the reduced model. The Deviance is the difference between the fitted or reduced model and the full model likelihood values. This deviance measures whether or not the smaller model (i.e., the fitted or reduced model) describe the data as well as the full model does. This deviance is then used to formulate a Chi-Square random variable that tests exactly that. The user may choose a rejection level (.05 is common) to test whether or not the model fit is appropriate. The p-value for testing whether or not the fitted model adequately describes the data is given next to the fitted model likelihood, and the user can reject or not reject a hypothesis according to the p-value given . The reduced model p-value would be used in the same way, but here the user would be testing whether or not there is in fact a dose/response relationship where the true population proportion is a function of dose, as opposed to a single population with one parameter (the proportion of affected animals).

Goodness of Fit Information - Litter Data and Grouped Data

Both of these tables provide a listing of the data, expected and observed responses and Chi-Square residuals (observed - expected). The "Litter Data" table contains this information for each litter. To obtain the "Group Data" table, the Litter Data were sorted on Dose (first), and by Litter Specific Covariate within Dose. Within dose, litters adjacent to each other with respect to Litter Specific Covariate were grouped together until the expected number of affected pups was at least one. This grouping was done prior to the estimation of an overall Chi-Square and p-value to improve the validity of the Chi-Square approximation for the goodness of fit statistic. Goodness of Fit statistics. Both tables list estimated probabilities, the expected and observed number of affected animals and Chi-Square residuals for each dose group. If a model fits well, the observed and expected number of affected animals should be relatively close. The overall Chi-Square value, and it corresponding p-value are an indication of that "closeness". If the p-value is larger than some predetermined critical p-value, then the user may be able to conclude that the model is appropriate to model the data.

The scaled residual values printed at the end of the table are defined as follows:

(Obs. - Expected)/sd,

where "Expected" is the expected number of responders from the model and sd equals the estimated standard deviation (square root of the estimated variance) of the expected number. For these models, the estimated variance is equal to n*p*(1-p) where n is the sample (litter) size and p is the model-predicted probability of response. The overall model should be called into question if the scaled residual value for any individual dose and litter-specific covariate combination, particularly for a low dose group, is greater than 2 or less than -2."

Benchmark Dose Computation

This is the ultimate goal of the BMDS software (see Overview). The BMD or BMDL is the value that the user will use when determining the RfD or RfC for the particular toxicant being studied. The user should investigate all the output to this point, and then make the decision to accept this as a valid BMDL.

4.4 Toxicodiffusion Model Text Output

The Toxicodiffusion model output file begins with a section that echoes user-specified information (e.g. Study Name and Study Description) as well as some information about the contents of the data set: what the dose levels are, at what times observations were available, and the sample size (i.e., the number of distinct combinations of experimental unit ID and time). The user should verify that these values are correct; if they are not, then the data file should be checked for data entry errors.
In addition, this section shows the form of the model.

Likelihood-Related Estimates
The AIC and BIC as well as the log-likelihood for the model fit to the data being analyzed are shown here.

Random Effects
This section shows which parameters were selected to have random effects around the main (fixed) effect. At this time, the only parameter for which random effects are specified is the parameter A_0 (the constant term in the background response polynomial). So, in this section there will be a standard deviation reflecting the variability of the random effects around the corresponding fixed effect. There will also be a "Residual" standard deviation reflecting the remaining variability that is not part of the random effect (reflecting the remaining lack of fit of the model to the data and therefore associated with residuals). The distributions of the random effects and of the residuals are assumed to be independent of one another. [At a later time, when more than one random effect is allowed, the distributions of the random effects will not be assumed to be independent of one another, though they all will still be assumed independent of the residual distribution. In the case of more than one random effect, pair-wise correlation estimates will be provided as well. When those correlations are close to 1 or -1, that may be a strong indication that the data cannot support that many random effects and alternative assumptions should be tried by the user.]

Parameter Estimates
In this section, the additional results related to the model fitting are provided. Parameter estimates for the fixed effects are shown with their standard errors. In addition the degrees of freedom, t-test statistic value, and associated p-value for that test are shown, in order to facilitate evaluation of the significance of the parameters.

In addition, parameter correlations and a summary of the within-group residuals are shown.

Initial Values

In this section one finds the set of initial values that were used when the model apparently converged to an acceptable answer. Below that is the list of the initial values that the model was scheduled to try; it starts with the first set listed and continues until it uses a set that resulted in apparent convergence.

BMD Estimation

In this section the summary BMD results are presented. First, the user-specified choices for risk type, spontaneous risk level (adverse level; if a Cut Point was used instead of Background Rate, then the value of the cut point would be printed here), the area of adverse effects (Adverse Direction), and the BMR level are shown. If these are not the choices the user wants to have, the option file should be revisited and correct values entered for these fields. The same is true of the number of bootstrap iteration which is shown next.

The minimum BMD is what is shown (the BMD, as a rule, varies as a function of time). The time at which that minimum BMD was obtained is also given. The value shown for "Confidence Level" is (1-α)*100% (where α is what was entered on the option screen). The lower limit presented is based on the user-specified number of bootstrap iterations. As discussed elsewhere, the user should test for stability of that estimate if the accuracy of the BMDL (or BMDU if that too is estimated) needs to be assured to some desired number of significant digits.

In addition to the text output file, five plots are produced with each run.

4.5 ten Berge Model Text Output

The ten Berge model output file begins with a section giving information about the version number and build date of the program, as well as identifying the input data set used to create the output and the name of the file that has the information needed to later produce graphics. [Currently, BMDS does not produce graphics for the ten Berge model.]

Model Specifications

This section provides the overview of the framework for the model, including the reference for Finney (1971) from which Wil ten Berge identified the probit analysis approach. The general form of the model as it is now implemented is presented here as is a basic summary of the number of input parameters (possible explanatory variables) and the number of observations in the data set.

Input Data Set Echo

This section should contain exactly the data that the user has included in the input file. If there are any errors here, the user should go back to the input file and correct the input values, and then rerun the analysis.

Modeling Choices

In this section, the following information is provided: the choices for the range of observations to analyze, the transformations of the input parameters to use, the link function (logit or probit), and the variable identifier numbers associated with the selected explanatory variables (single input parameters or products of pairs of input parameters). If any of this information does not correspond to the desired analysis, the user must go back to the input file to make corrections to the coding in the modeling section.

Fit and Parameter Estimates

The chi-square evaluation of fit and the degrees of freedom associated with the model fit to the selected data are given. The fit is assessed in relation to the "saturated" model having as many parameters as observations. The maximum likelihood estimates of the B_i coefficients are shown as is a Student t value

that can be used to determine whether each of those terms is "statistically significant." Variance and covariance estimates for each of the B_i terms are provided.

Notes: When the model fails, one or more of the parameter values may have a value of the form "-1.#J" or a similar non-number. This is an indication that the model has not converged to an answer. The user should check the input file (also reflected in the data echo section of the output file) to see if some data entry errors are contributing to that problem.

If there are no errors in the input data, it is entirely possible that there is no solution for some data; this happens, for example, when there are only groups with either 0% or 100% response. In such cases, the model cannot determine a maximum likelihood and returns values for one or more of the parameters (and estimates depending on those parameters) that are of the form "-1.#IOe+000," "1.#R," "1.#QOe+000," "1.#QNAN0," or similar indications that no numerical answer was available. It is known, for example, that probit slope estimates can be infinite in some situations where concentrations with and without response are not suitably intermingled. A sufficient (but not necessary) condition to avoid this is to have two distinct doses with partial response.

"Dose" Estimation

In this section one finds the estimate of an input variable value that, for a given response and for specified values of the other input parameters, gives that response rate. Confidence limits are estimated if requested. Some reviewers have strongly suggested that the Student T-based deviates always be used and (confidence intervals obtained when a standard normal deviate is used are "too tight") and so one might want to obtain from statistical tables the deviate for a T-distribution having degrees of freedom equal to the number of observations minus the number of estimated parameters (e.g., the 95th percentile from such a T-distribution). These same comments also apply to the next two sections giving estimates and confidence intervals for response rates and for the ratios of model parameters.

Notes: The use of the terminology "probability of correct model" in the output file is not a good choice for describing the results of the chi-squared goodness-of-fit test that is the basis for the reported p-value. Subsequent versions of this software will replace that terminology with a statement like "The p-value associated with the chi-square goodness of fit test equals x" where x is the calculated p-value. The terminology as shown in the example output file has been retained so that comparisons between the new version and the original version of the ten Berge software could be more easily made (the same description has been retained in both cases). Similarly, the statement that the "prediction of the model is not sufficient" will be modified to simply indicate whether or not the p-value is greater than or less than 0.05, with the appropriate statement regarding adequate fit of the model or not (similar to the evaluations of fit in other BMDS models) and a suggestion that (if the model is not fitting the data well) the correction factor be applied to the variance and covariance estimates as well as selecting the deviate from the Student T distribution rather than the standard normal distribution. Currently, neither the variance-covariance correction nor the choice of the deviate are done automatically for the calculation of confidence limits.

Response Estimation

Much like the previous section, this section provides estimates of the response associated with specified values of the input variables used in the model. When a deviate is given, the corresponding confidence interval is also calculated for that estimate. Note that the deviate supplied need not be the same as the one provided for the "dose" estimation, in case different confidence levels may be desired for dose and response estimates.

Notes: See notes in previous section about terminology related to the model fit.

Ratio Estimation

In this section the ratio of the Bi coefficients request by the user will be reported. As in the previous sections the confidence interval is also shown, if requested, at a level consistent with the specified deviate.

Notes: See notes in previous section about terminology related to the model fit.

5 GRAPHIC OUTPUT FROM MODELS

The graphic output plot should display along with the text output file after each model run. The BMD and BMDL are identified on the plot as green vertical lines and are associated with the response level associated with the user selected BMR, the horizontal green line. The BMD curve estimated by the model is represented by a red line and the BMDL curve (which is basically just connecting 5 BMDL estimates) is represented by the blue line. Data points are shown in green with their individual group confidence intervals.

The graphic display features can be modified by either using WGNUPlot edit features or copying the plot to your computer's clip board and pasting it into another application capable of performing vector graphic editing (e.g., Microsoft PowerPoint). These copy and edit features are accessible by left-clicking on the small graphic icon at the top of the plot page or right-clicking on the graph. A menu will appear which allows you to modify the plot window in various ways. Among the "Options" available are copying to the clipboard, changing background, color and font specifications, and printing. Under the "Print" option, you can choose to print landscape or portrait. Various sizing options are then offered, which should allow for full page, and other displays options.

6 ACRONYMS, TERMS, AND DEFINITIONS

ACRONYM	EXPANDED
BMDS	Benchmark Dose Software
BMR	Benchmark Response
CatReg	Categorical Regression
CRAN	Comprehensive R Archive Network
CSF	Cancer Slope Factor
EPA	Environmental Protection Agency
IRIS	Integrated Risk Information System
IT	Information Technology
ITS-ESE	Information Technology Solutions- Environmental System Engineering
LM ES&S	Lockheed Martin Enterprise Solutions & Services
NCEA	National Center for Environmental Assessment
NIST	National Institute of Standards Technology
ORD	Office of Research and Development
PROAST	Continuous Exponential Model
RIVM	National Institute for Public Health and the Environment (Netherlands)
RfC	Reference Concentrations
RfD	Reference Doses
RTP	Research Triangle Park
TO	Task Order
TOPO	Task Order Project Officer

7 REFERENCES

1. Crump, K. 1984. A new method for determining allowable daily intakes. Fund. Appl. Toxicol. 4: 854-871.
2. Kimmel, C.; Gaylor, D. 1988. Issues in qualitative and quantitative risk analysis for developmental toxicology. Risk Anal. 8: 15-21.
3. U.S. EPA. 1995. The use of the benchmark dose approach in health risk assessment. Office of Research and Development, Washington, DC: EPA/630/R-94/007, February, 1995.
4. Crump, K.S., D.G. Hoel, C.H. Langley and R. Peto. 1976. Fundamental carcinogenic processes and their implications for low-dose risk assessment. Cancer Research 36:2973-2979.
5. Hoel, D.G. 1980. Incorporation of background in dose-response models. Federation Proceedings 39(1): 73-75.
6. Krewski, D., and J. van Ryzin. 1981. Dose response models for quantal response toxicity data. pp. 201-231 IN: Statistics and Related Topics. Proc. International Symposium on Statistics and Related Topics, Ottawa, May 5-7, 1980. Eds. M Csorgo, D.A. Dawson, J.N.K. Rao, and A.K.Md.E. Saleh Amsterdam: North-Holland.
7. NRC (National Research Council). 1980. Drinking Water and Health, volume 3. Washington, DC : National Academy Press.

8 APPENDICES

8.1 Model Input Files Format

Each model listed above is a separate executable file that makes use of DOS text input files. The DOS text files provide the "instructions" for the model run. The BMDS interface software assists users in the creation of properly formatted input files for the model executables. The text file format for these data input files are model specific and can be obtained by following the Related Topics links above. Each model can be run from the DOS command line of your computer by typing the model file name followed by the complete name (including directory location and extension) of an associate data input file (BMDS expects these files to be labeled with a .(d) extension, but the model executables will accept any extension).

The model will generate both a text output (.out) and a graphic (.002) file with the same name prefix as the .(d) file. The .out file can be read with any text editor. The BMDS interface automatically creates a plot (.plt) file from the .002 file and displays it using the GNUPlot program you should have installed with BMDS. Plot files can also be created from the DOS command line of your computer by typing the name of the scripter file associated with the continuous (00*.exe), nested (05*.exe) or dichotomous (10*.exe) model that was used, followed by the complete name (including directory location and extension) of the .002 file associated with the model run. The wgnupl32.exe program included with the BMDS installation can then be used to view or edit the plot (.plt) file.

BMDS 2.0 operates in a Windows environment and automatically performs the DOS process commands when a session is run.

Cancer Dichotomous Model Input File Format

[1] Model name, in this case, the string Multistage-Cancer

[2] User notes

[3] Input file name

[4] Output file name

[5] Number of Observations

[6] Degree of Polynomial

[7a] Maximum # of iterations

= Default of 250 if user does not input a value
= User input value otherwise

[7b] Rel Function Convergence

= Default of 2.22045e-16 if user does not input a value
= User input value otherwise

[7c] Parameter Convergence
= Default of 1.49012e-8 if user does not input a value
= User input value otherwise

[8] BMDL Curve Calculation
= 1 if BMDL Curve Calculation box is checked
= 0 otherwise

[9] Restrict Betas >= 0
= 1 if Restrict Betas >= 0 box is checked
= 0 otherwise

NOTE: In the cancer model, this parameter will always be set equal to 1.

[10] BMD Calculation
= 1 if BMD calculation box is checked
= 0 otherwise

[11] Append or Overwrite Output File
= 1 if Append is selected
= 0 if Overwrite is selected
NOTE: This parameter is automatically set to 0 by the user interface and can only be changed by manually editing the .(d) file!!!!

[12] Smooth Option
= 0 if Unique
= 1 if C-Spline

[13] BMR (BMR level)
= User input value (or default of .100)

[14] Risk Type
= 0 if Extra
= 1 if Added

[15] Confidence Level
= User input value (or default of .950)

[16] Background Parameter
= User input value if Specified Option is selected
= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[17] Beta1 Parameter
= User input value if Specified Option is selected
= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[18] Beta2 Parameter
= User input value if Specified Option is selected
= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[18+] Etc. for Beta3, Beta4...
= User input value if Specified Option is selected
= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[19] Initialize Parameters
= 1 if one or more parameters are set to initialized
= 0 otherwise

[20] Background Parameter
= User specified initial value if "initialized" is selected for this parameter
= -9999 if "initialized" is not selected

[21] Beta1 Parameter
= User specified initial value if "initialized" is selected for this parameter
= -9999 if "initialized" is not selected

[22] Beta2 Parameter
= User specified initial value if "initialized" is selected for this parameter
= -9999 if "initialized" is not selected

[22+] Etc. for Beta3, Beta4,...as necessary

[23] Dose Name

[24] Response Name

[25] Constant String: NEGATIVE_RESPONSE

Data:

Dose in first column
Response in Second
Total minus Response in third column

Example Format

[1] Multistage

[2] BMDS MODEL RUN

[3] EXAMPLE.SET

[4] EXAMPLE

[5] 4

[6] 2

[7a]	[7b]	[7c]	[8]	[9]	[10]	[11]	[12]
250	2.22045e-16	1.49012e-8	1	1	0	1	1

[13]	[14]	[15]
0.10	0	0.95

[16]	[17]	[18+]
-9999	-9999	-9999 ...

[19] 0

[20]	[21]	[22+]
-9999	-9999	-9999 ...

[23]	[24]	[25]

Dose	Resp	NEGATIVE_RESPONSE
0	3	47
50	6	44
100	10	40
150	19	31

Gamma Dichotomous Model Input File Format

[1] Model name, in this case, the string Gamma

[2] User notes

[3] Input file name

[4] Output file name

[5] Number of Observations

[6a] Maximum # of iterations

= Default of 250 if user does not input a value
= User input value otherwise

[6b] Rel Function Convergence

= Default of 2.22045e-16 if user does not input a value
= User input value otherwise

[6c] Parameter Convergence.

= Default of 1.49012e-8 if user does not input a value
= User input value otherwise

[7] BMDL Curve Calculation

= 1 if BMDL Curve Calculation box is checked
= 0 otherwise

[8] Restrict Power >= 1

= 1 if Restrict Power >= 1 box is checked
= 0 otherwise

[9] BMD Calculation

= 1 if BMD calculation box is checked
= 0 otherwise

[10] Append or Overwrite Output File

= 1 if Append is selected
= 0 if Overwrite is selected

NOTE: This parameter is automatically set to 0 by the user interface and can only be changed by manually editing the .(d) file!!!!

[11] Smooth Option

= 0 if Unique
= 1 if C-Spline

[12] BMR (BMR level)

= User input value (or default of .100)

[13] Risk Type

= 0 if Extra
= 1 if Added

[14] Confidence Level

= User input value (or default of .950)

[15] Background Parameter

= User input value if Specified Option is selected
= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[16] Slope Parameter

= User input value if Specified Option is selected
= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[17] Power Parameter

= User input value if Specified Option is selected
= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[18] Initialize Parameters

= 1 if one or more parameters are set to initialized
= 0 otherwise

[19] Background Parameter.

= User specified initial value if "initialized" is selected for this parameter
= -9999 if "initialized" is not selected

[20] Slope Parameter

= User specified initial value if "initialized" is selected for this parameter
= -9999 if "initialized" is not selected

[21] Power Parameter

= User specified initial value if "initialized" is selected for this parameter
= -9999 if "initialized" is not selected

[22] Dose Name

[23] Response Name

[24] Constant String: NEGATIVE_RESPONSE

Data:

Dose in first column
Response in Second
Total minus Response in third column

Example Format

[1] Gamma

[2] BMDS MODEL RUN

[3] EXAMPLE.SET

[4] EXAMPLE

[5] 4

[6a]	[6b]	[6c]	[7]	[8]	[9]	[10]	[11]
250	2.22045e-16	1.49012e-8	1	1	1	1	0

[12]	[13]	[14]
0.10	0	0.95

[15]	[16]	[17]
-9999	-9999	-9999

[18] 0

[19]	[20]	[21]
-9999	-9999	-9999

[22]	[23]	[24]
Dose	Resp	NEGATIVE_RESPONSE
0	3	47
50	6	44
100	10	40
150	19	31

Hill Continuous Model Input File Format

[1] Model Name, in this case, the constant string Hill

[2] User Notes

[3] Input file name

[4] Output data file name

[5] Input Type

= 1 if entered as group data (e.g., Dose, N, Mean, Std.)
= 0 if individual animal data (e.g., Dose, Response) is entered

[6] A count of the number of observations

[7] Adverse Direction

= 0 if Automatic (adverse direction with increasing dose estimated by model)
= 1 if Up (dose-response curve trends up with increasing dose)
= -1 if Down (dose-response curve trends down with increasing dose)

[8a] Maximum # of iterations

= Default of 250 if user does not input a value
= User input value otherwise

[8b] Rel Function Convergence

= Default of 2.22045e-16 if user does not input a value
= User input value otherwise

[8c] Parameter Convergence.

= Default of 1.49012e-8 if user does not input a value
= User input value otherwise

[9] BMDL Curve Calculation

= 1 if BMDL Curve Calculation box is checked
= 0 otherwise

[10] Restrict n > 1?

= 1 if Restrict n > 1 box is checked
= 0 otherwise

[11] BMD Calculation

= 1 if BMD calculation box is checked
= 0 otherwise

[12] Append or Overwrite Output File

= 1 if Append is selected
= 0 if Overwrite is selected

NOTE: This parameter is automatically set to 0 by the user interface andcan only be changed by manually editing the .(d) file!!!!

[13] Smooth Option

= 0 if Unique
= 1 if C-Spline

[14] BMR Type

= 0 if Absolute Dev.
= 1 if Std. Dev.
= 2 if Relative Dev.(Default)
= 3 if Point
= 4 if Extra

[15] BMR (BMR Level)

= User input value (Default = 0.1000)

[16] Constant Variance

= 0 if not (the variance is to be modeled as Var(i) = alpha*mean(i)^rho)
= 1 if box is checked (rho is set to 0 in the above equation)

[17] Confidence Level

= User input value (or default of .950)

[18] Alpha Parameter

= User input value if Specified Option is selected
= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[19] Rho Parameter

= 0 if Constant Variance box is checked

If Constant Variance box not checked,

= User input value if Specified Option is selected
= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[20] Intercept Parameter

= User input value if Specified Option is selected
= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[21] v Parameter

= User input value if Specified Option is selected
= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[22] n Parameter

= User input value if Specified Option is selected
= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[23] k Parameter

= User input value if Specified Option is selected
= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[24] Initialize Parameters

= 1 if one or more parameters are set to initialized
= 0 otherwise

[25] Alpha Parameter

= User specified initial value if "initialized" is selected for this parameter
= -9999 if not checked

[26] Rho Parameter

= User specified initial value if "initialized" is selected for this parameter
= -9999 if not checked

[27] Intercept Parameter

= User specified initial value if "initialized" is selected for this parameter
= -9999 if not checked

[28] v Parameter

= User specified initial value if "initialized" is selected for this parameter
= -9999 if not checked

[29] n Parameter

= User specified initial value if "initialized" is selected for this parameter
= -9999 if not checked

[30] k Parameter

= User specified initial value if "initialized" is selected for this parameter
= -9999 if not checked

[31]-[34] IN THIS ORDER, by checking the column assignment pull down menus, these fields should contain:

If Group data is entered:

[31]	[32]	[33]	[34]
Dose name	N name	Mean Name	Std Name

If Individual data is entered:

[31]	[32]

Dose name Response name etc.

In the same column order as above, this should just be a data listing.

Example Format

[1] Hill

[2] BMDS MODEL RUN

[3] HYBRID1.SET

[4] HYBRID1

[5]	[6]	[7]
1	6	1

[8a]	[8b]	[8c]	[9]	[10]	[11]	[12]	[13]
250	2.22045 e-16	1.49012 e-8	1	0	1	1	1

[14]	[15]	[16]	[17]
1	1.00	1	095

[18]	[19]	[20]	[21]	[22]	[23]
-9999	-9999	-9999	-9999	-9999	-9999

[24] 0

[25]	[26]	[27]	[28]	[29]	[30]
-9999	-9999	-9999	-9999	-9999	-9999

[31]	[32]	[33]	[34]
DOSE	NI	MEAN	STD
0	4	38.45	1.1683
8	5	39.56	1.28218
20	4	40.9	1.303
30	4	41.95	1.418203
40	4	42.725	1.438
50	5	43.42	1.45932

Linear Continuous Model Input File Format

Use Polynomial Continuous Model Input File Format, but make sure the polynomial degree (Item 4a) is set to 1.

Logistic and Log-Logistic Dichotomous Model Input File Format

[1] Model name, in this case, the string Logist

[2] User notes

[3] Input file name

[4] Output file name

[5] Number of Observations

[6a] Maximum # of iterations

= Default of 250 if user does not input a value
= User input value otherwise

[6b] Rel Function Convergence

= Default of 2.22045e-16 if user does not input a value
= User input value otherwise

[6c] Parameter Convergence

= Default of 1.49012e-8 if user does not input a value
= User input value otherwise

[7] BMDL Curve Calculation

= 1 if BMDL Curve Calculation box is checked
= 0 otherwise

[8] Log Transformation

= 1 if Log transformation is to be used
= 0 otherwise

[9] Restrict Slope >= 1

= 1 if Restrict Slope >= 1 box is checked
= 0 otherwise

[10] BMD Calculation

= 1 if BMD calculation box is checked
= 0 otherwise

[11] Append or Overwrite Output File

= 1 if Append is selected
= 0 if Overwrite is selected

NOTE: This parameter is automatically set to 0 by the user interface and can only be changed by manually editing the .(d) file!!

[12] Smooth Option

= 0 if Unique
= 1 if C-Spline

[13] BMR (BMR level)

= User input value (or default of .100)

[14] Risk Type

= 0 if Extra
= 1 if Added

[15] Confidence Level

= User input value (or default of .950)

[16] Background Parameter

= User input value if Specified Option is selected
= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value or if Log transformation not selected

[17] Slope Parameter

= User input value if Specified Option is selected
= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[18] Intercept Parameter

= User input value if Specified Option is selected
= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[19] Initialize Parameters

= 1 if one or more parameters are set to initialized
= 0 otherwise

[20] Background Parameter

= User specified initial value if "initialized" is selected for this parameter
= -9999 if "initialized" is not selected or if Log transformation not selected

[21] Slope Parameter

= User specified initial value if "initialized" is selected for this parameter
= -9999 if "initialized" is not selected

[22] Intercept Parameter

= User specified initial value if "initialized" is selected for this parameter
= -9999 if "initialized" is not selected

[23] Dose Name

[24] Response Name

[25] Constant String: NEGATIVE_RESPONSE

Data:

Dose in first column
Response in Second
Total minus Response in third column

Example Format

[1] Logist

[2] BMDS MODEL RUN

[3] EXAMPLE.SET

[4] EXAMPLE

[5] 4

[6a]	[6b]	[6c]	[7]	[8]	[9]	[10]	[11]	[12]
250	2.22045e-16	1.49012e-8	1	0	0	1	1	0

[13]	[14]	[15]
0.10	0	0.95

[16]	[17]	[18]
-9999	-9999	-9999

[19] 0

[20]	[21]	[22]
-9999	-9999	-9999

[23]	[24]	[25]
Dose	Resp	NEGATIVE_RESPONSE
0	3	47
50	6	44
100	10	40
150	19	31

Logistic Nested Model Input File Format

[1] Model name, in this case, the string Nlogist

[2] User notes

[3] Input file name

[4] Output file name

[5] Number of Observations

[5a] Number of Dose groups

[6a] Maximum # of iterations
= Default of 250 if user does not input a value
= User input value otherwise

[6b] Rel Function Convergence
= Default of 2.22045e-16 if user does not input a value
= User input value otherwise

[6c] Parameter Convergence.
= Default of 1.49012e-8 if user does not input a value
= User input value otherwise

[7] BMDL Curve Calculation
= 1 if BMDL Curve Calculation box is checked
= 0 otherwise

[8] Restrict Power >= 1 (Note: Power = Rho parameter in model)
= 1 if Restrict Power >= 1 box is checked
= 0 otherwise

[9] BMD Calculation
= 1 if BMD calculation box is checked
= 0 otherwise

[10] Fixed Size
= 1 if Ctrl Group Mean selected

= 0 if overall mean selected

[11] Append or Overwrite Output File

= 1 if Append is selected

= 0 if Overwrite is selected

NOTE: This parameter is automatically set to 0 by the user interface and can only be changed by manually editing the .(d) file!!!!

[12] Smooth Option

= 0 if Unique

= 1 if C-Spline

[13] BMR (BMR level)

= User input value (or default of .100)

[14] Risk Type

= 0 if Extra

= 1 if Added

[15] Confidence Level

= User input value (or default of .950)

[16] Alpha Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[17] Rho Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[18] Beta Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[19] Theta1 Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[20] Theta2 Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[21] Phi1 Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[22] Phi2 Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[23] Phi3 Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[24] Phi4 Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[24+] Phi5 through Phi10 if necessary (as many Phi parameters as dose groups)

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[25] Initialize Parameters

= 1 if one or more parameters are set to initialized

= 0 otherwise

[26] Alpha Parameter

= User specified initial value if "initialized" is selected for this parameter

= -9999 if not checked

[27] Rho Parameter

= User specified initial value if "initialized" is selected for this parameter

= -9999 if not checked

[28] Beta Parameter

= User specified initial value if "initialized" is selected for this parameter

= -9999 if not checked

[29] Theta1 Parameter

= User specified initial value if "initialized" is selected for this parameter

= -9999 if not checked

[30] Theta2 Parameter

= User specified initial value if "initialized" is selected for this parameter

= -9999 if not checked

[31] Phi1 Parameter

= User specified initial value if "initialized" is selected for this parameter

= -9999 if not checked

[32] Phi2 Parameter

= User specified initial value if "initialized" is selected for this parameter

= -9999 if not checked

[33] Phi3 Parameter

= User specified initial value if "initialized" is selected for this parameter

= -9999 if not checked

[34] Phi4 Parameter

= User specified initial value if "initialized" is selected for this parameter

= -9999 if not checked

[34+] Phi5 through Phi10 if necessary (as many Phi parameters as dose groups)

= User specified initial value if "initialized" is selected for this parameter

= -9999 if not checked

[35] Dose Name

[36] Response Name

[37] Constant String: NEGATIVE_RESPONSE

[38] Column 4 name

[39] Column 5 name

Data:

Dose in first column
Response in Second
Total (Litter Size) minus Response in third column
Litter Size
Group number, or anything you want, really, so long as its integers

Example Format

[1] Nlogist

[2] BMDS MODEL RUN

[3] NCTR31.SET

[4] NCTR31

[5]	[5a]
40	4

[6a]	[6b]	[6c]	[7]	[8]	[9]	[10]	[11]	[12]
250	2.22045 e-16	1.49012 e-8	1	0	1	1	1	0

[13]	[14]	[15]
0.05	0	0.95

[16]	[17]	[18]	[19]	[20]
-9999	-9999	-9999	-9999	-9999

[21]	[22]	[23]	[24+]
-9999	-9999	-9999	-9999

[25] 0

[26]	[27]	[28]	[29]	[30]

-9999 -9999 -9999 -9999 -9999

[31] [32] [33] [34+]
-9999 -9999 -9999 -9999

[35]	[36]	[37]	[38]	[39]
Dose	resp	nega_resp	column4	column5
0	0	13	13	
0	4	10	14	
0	1	12	13	
0	2	10	12	
0	2	10	12	
0	2	9	11	
0	2	5	7	
0	0	12	12	
0	2	10	12	
0	0	9	9	
25	4	9	13	
25	4	8	12	
25	3	11	14	
25	7	3	10	
25	5	6	11	
25	3	9	12	
25	1	11	12	
25	5	8	13	
25	3	8	11	
25	5	11	16	
50	3	6	9	
50	10	6	16	
50	10	3	13	
50	3	5	8	
50	5	4	9	
50	7	4	11	
50	5	3	8	
50	3	9	12	
50	8	3	11	
50	6	3	9	
100	10	4	14	
100	2	1	3	
100	13	1	14	
100	3	3	6	
100	10	1	11	

100	9	1	10
100	9	1	10
100	6	3	9
100	5	4	9
100	7	2	9

Multistage Dichotomous Model Input File Format

[1] Model name, in this case, the string Multistage

[2] User notes

[3] Input file name

[4] Output file name

[5] Number of Observations

[6] Degree of Polynomial

[7a] Maximum # of iterations

= Default of 250 if user does not input a value
= User input value otherwise

[7b] Rel Function Convergence

= Default of 2.22045e-16 if user does not input a value
= User input value otherwise

[7c] Parameter Convergence

= Default of 1.49012e-8 if user does not input a value
= User input value otherwise

[8] BMDL Curve Calculation

= 1 if BMDL Curve Calculation box is checked
= 0 otherwise

[9] Restrict Betas >= 0

= 1 if Restrict Betas >= 0 box is checked
= 0 otherwise

[10] BMD Calculation

= 1 if BMD calculation box is checked
= 0 otherwise

[11] Append or Overwrite Output File

= 1 if Append is selected
= 0 if Overwrite is selected

NOTE: This parameter is automatically set to 0 by the user interface and can only be changed by manually editing the .(d) file!!!!

[12] Smooth Option

= 0 if Unique
= 1 if C-Spline

[13] BMR (BMR level)

= User input value (or default of .100)

[14] Risk Type

= 0 if Extra
= 1 if Added

[15] Confidence Level

= User input value (or default of .950)

[16] Background Parameter

= User input value if Specified Option is selected
= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[17] Beta1 Parameter

= User input value if Specified Option is selected
= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[18] Beta2 Parameter

= User input value if Specified Option is selected
= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[18+] Etc. for Beta3, Beta4...

= User input value if Specified Option is selected
= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[19] Initialize Parameters

= 1 if one or more parameters are set to initialized
= 0 otherwise

[20] Background Parameter

= User specified initial value if "initialized" is selected for this parameter
= -9999 if "initialized" is not selected

[21] Beta1 Parameter

= User specified initial value if "initialized" is selected for this parameter
= -9999 if "initialized" is not selected

[22] Beta2 Parameter

= User specified initial value if "initialized" is selected for this parameter
= -9999 if "initialized" is not selected

[22+] Etc. for Beta3, Beta4,...as necessary

[23] Dose Name

[24] Response Name

[25] Constant String: NEGATIVE_RESPONSE

Data:

Dose in first column
Response in Second
Total minus Response in third column

Example Format

[1] Multistage

[2] BMDS MODEL RUN

[3] EXAMPLE.SET

[4] EXAMPLE

[5]	[6]
4	2

[7a]	[7b]	[7c]	[8]	[9]	[10]	[11]	[12]
250	2.22045e-16	1.49012e-8	1	0	0	1	1

[13]	[14]	[15]
0.10	0	0.95

[16]	[17]	[18+]
-9999	-9999	-9999 ...

[19] 0

[20]	[21]	[22+]
-9999	-9999	-9999 ...

[23]	[24]	[25]
Dose	Resp	NEGATIVE_RESPONSE
0	3	47
50	6	44
100	10	40
150	19	31

NCTR Nested Model Input File Format

[1] Model name, in this case, the string NCTR

[2] User notes

[3] Input file name

[4] Output file name

[5] Number of Observations

[5a] Number of Dose groups

[6a] Maximum # of iterations

= Default of 250 if user does not input a value

= User input value otherwise

[6b] Rel Function Convergence

= Default of 2.22045e-16 if user does not input a value

= User input value otherwise

[6c] Parameter Convergence

= Default of 1.49012e-8 if user does not input a value

= User input value otherwise

[7] BMDL Curve Calculation

= 1 if BMDL Curve Calculation box is checked

= 0 otherwise

[8] Restrict Power >= 1 (Note: Power = Rho parameter in model)

= 1 if Restrict Power >= 1 box is checked

= 0 otherwise

[9] BMD Calculation

= 1 if BMD calculation box is checked

= 0 otherwise

[10] Fixed Size

= 1 if Ctrl Group Mean selected

= 0 if overall mean selected

[11] Append or Overwrite Output File

= 1 if Append is selected

= 0 if Overwrite is selected

NOTE: This parameter is automatically set to 0 by the user interface and can only be changed by manually editing the .(d) file!!

[12] Smooth Option

= 0 if Unique

= 1 if C-Spline

[13] BMR (BMR level)

= User input value (or default of .100)

[14] Risk Type

= 0 if Extra

= 1 if Added

[15] Confidence Level

= User input value (or default of .950)

[16] Alpha Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[17] Rho Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[18] Beta Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[19] Theta1 Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[20] Theta2 Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[21] Phi1 Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[22] Phi2 Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[23] Phi3 Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[24] Phi4 Parameter

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[24+] Phi5 through Phi10 if necessary (as many Phi parameters as dose groups)

= User input value if Specified Option is selected

= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[25] Initialize Parameters

= 1 if one or more parameters are set to initialized

= 0 otherwise

[26] Alpha Parameter

= User specified initial value if "initialized" is selected for this parameter

= -9999 if not checked

[27] Rho Parameter

= User specified initial value if "initialized" is selected for this parameter

= -9999 if not checked

[28] Beta Parameter

= User specified initial value if "initialized" is selected for this parameter

= -9999 if not checked

[29] Theta1 Parameter

= User specified initial value if "initialized" is selected for this parameter

= -9999 if not checked

[30] Theta2 Parameter

= User specified initial value if "initialized" is selected for this parameter

= -9999 if not checked

[31] Phi1 Parameter

= User specified initial value if "initialized" is selected for this parameter

= -9999 if not checked

[32] Phi2 Parameter

= User specified initial value if "initialized" is selected for this parameter

= -9999 if not checked

[33] Phi3 Parameter

= User specified initial value if "initialized" is selected for this parameter

= -9999 if not checked

[34] Phi4 Parameter

= User specified initial value if "initialized" is selected for this parameter

= -9999 if not checked

[34+] Phi5 through Phi9 if necessary (as many Phi parameters as dose groups)

= User specified initial value if "initialized" is selected for this parameter

= -9999 if not checked

[35] Dose Name

[36] Response Name

[37] Constant String: NEGATIVE_RESPONSE

[38] Column 4 name

Data:

Dose in first column
Response in Second
Total (Litter Size) minus Response in third column
Litter Size

Example Format

[1] NCTR

[2] BMDS MODEL RUN

[3] NCTR31.SET

[4] NCTR31

[5]	[5a]
40	4

[6a]	[6b]	[6c]	[7]	[8]	[9]	[10]	[11]	[12]

250	2.22045 e-16	1.49012 e-8	1	0	1	1	1	0

[13]	[14]	[15]
0.05	0	0.95

[16]	[17]	[18]	[19]	[20]
-9999	-9999	-9999	-9999	-9999

[21]	[22]	[23]	[24+]
-9999	-9999	-9999	-9999

[25] 0

[26]	[27]	[28]	[29]	[30]
-9999	-9999	-9999	-9999	-9999

[31]	[32]	[33]	[34+]
-9999	-9999	-9999	-9999

[35]	[36]	[37]	[38]
Dose	resp	nega_resp	column4
0	0	13	13
0	4	10	14
0	1	12	13
0	2	10	12
0	2	10	12
0	2	9	11
0	2	5	7
0	0	12	12
0	2	10	12
0	0	9	9
25	4	9	13
25	4	8	12
25	3	11	14
24	7	3	10
25	5	6	11
25	3	9	12
25	1	11	12
25	5	8	13
25	3	8	11
25	5	11	16
50	3	6	9
50	10	6	16
50	10	3	13

50	3	5	8
50	5	4	9
50	7	4	11
50	5	3	8
50	3	9	12
50	8	3	11
50	6	3	9
100	10	4	14
100	2	1	3
100	13	1	14
100	3	3	6
100	10	1	11
100	9	1	10
100	9	1	10
100	6	3	9
100	5	4	9
100	7	2	9

Polynomial Continuous Model Input File Format

[1] Model Name, in this case, the constant string Polynomial

[2] User Notes

[3] Input file name

[4] Output data file name

[4a] Degree of polynomial

= Default of 2 if user does not input a value
= 1 if Linear model is chosen
= User input value otherwise

[5] Input type

= 1 if entered as group data (e.g., Dose, N, Mean, Std.)
= 0 if individual animal data (e.g., Dose, Response) is entered

[6] A count of the number of observations

[7] Adverse direction

= 0 if Automatic (adverse direction with increasing dose estimated by model)
= 1 if Up (dose-response curve trends up with increasing dose)
= -1 if Down (dose-response curve trends down with increasing dose)

[8a] Maximum # of iterations

= Default of 250 if user does not input a value
= User input value otherwise

[8b] Rel Function Convergence

= Default of 2.22045e-16 if user does not input a value

= User input value otherwise

[8c] Parameter Convergence.

= Default of 1.49012e-8 if user does not input a value
= User input value otherwise

[9] BMDL Curve Calculation

= 1 if BMDL Curve Calculation box is checked
= 0 otherwise

[10] Restriction on polynomial coefficients

= 0 if none
= -1 if non-positive
= 1 if non-negative

[11] BMD Calculation

= 1 if BMD calculation box is checked
= 0 otherwise

[12] Append or Overwrite Output File

= 1 if Append is selected
= 0 if Overwrite is selected

NOTE: This parameter is automatically set to 0 by the user interface and can only be changed by manually editing the .(d) file!!!!

[13] Smooth Option

= 0 if Unique
= 1 if C-Spline

[14] BMR Type

= 0 if Absolute Dev.
= 1 if Std. Dev
= 2 if Relative Dev.(Default)
= 3 if Point
= 4 if Extra

[15] BMR (BMR Level)

= User input value (or default of 0.1)

[16] Constant Variance

= 0 if not (the variance is to be modeled as Var(i) = alpha*mean(i)^rho)
= 1 if box is checked (rho is set to 0 in the above equation)

[17] Confidence Level

= User input value (or default of .950)

[18]-[22+] Parameter values, either user specified or default values. If the parameter is not specified, the default value is -9999

[18] Alpha Parameter

= User input value if Specified Option is selected
= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[19] Rho Parameter

= 0 if Constant Variance box is checked

If Constant Variance box not checked,

= user input value if Specified Option is selected
= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[20]-[22+] Beta parameters in order of appearance on run screen.

= User input value if Specified Option is selected
= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[23] Initialize Parameters

= 1 if one or more parameters are set to initialized
= 0 otherwise

[24] Alpha Parameter

= User specified initial value if "initialized" is selected for this parameter
= -9999 if not checked

[25] Rho Parameter

= User specified initial value if "initialized" is selected for this parameter
= -9999 if not checked

[26]-[28+] Beta parameters in order of appearance on run screen

= User specified initial value if "initialized" is selected for this parameter
= -9999 if not checked

[29]-[32] IN THIS ORDER, by checking the column assignment pull down menus, these fields should contain:

If Group data is entered:

[29]	[30]	[31]	[32]
Dose name	N name	Mean Name	Std Name

If Individual data is entered:

[29]	[30]
Dose name	Response name

In the same column order as above, this should just be a data listing.

Example Format

[1] Polynomial

[2] BMDS MODEL RUN

[3] Poly1.SET

[4] Poly

[4a] 2

[5]	[6]	[7]
1	6	0

[8a]	[8b]	[8c]	[9]	[10]	[11]	[12]	[13]
250	2.22045e-16	1.49012e-8	1	0	1	1	0

[14]	[15]	[16]	[17]
1	1.00	1	0.95

[18]	[19]	[20]	[21]	[22 +...]
-9999	-9999	-9999	-9999	-9999

[23] 0

[24]	[25]	[26]	[27]	[28 +...]
-9999	-9999	-9999	-9999	-9999

[29]	[30]	[31]	[32]
DOSE	NI	MEAN	STD
0	4	38.45	1.1683
8	5	39.56	1.28218
20	4	40.9	1.303
30	4	41.95	1.418203
40	4	42.725	1.438
50	5	43.42	1.45932

Power Continuous Model Input File Format

[1] Model Name, in this case, the constant string Power

[2] User Notes

[3] Input file name

[4] Output data file name

[5] Input Type

= 1 if entered as group data (e.g., Dose, N, Mean, Std.)
= 0 if animal data (e.g., Dose, Response) is entered

[6] A count of the number of observations

[7] Adverse Direction

= 0 if Automatic (adverse direction with increasing dose estimated by model)
= 1 if Up (dose-response curve trends up with increasing dose)
= -1 if Down (dose-response curve trends down with increasing dose)

[8a] Maximum # of iterations

= Default of 250 if user does not input a value
= User input value otherwise

[8b] Rel Function Convergence

= Default of 2.22045e-16 if user does not input a value
= User input value otherwise

[8c] Parameter Convergence.

= Default of 1.49012e-8 if user does not input a value
= User input value otherwise

[9] BMDL Curve Calculation

= 1 if BMDL Curve Calculation box is checked
= 0 otherwise

[10] Restrict power >= 1

= 1 if Restrict Power >= 1 box is checked
= 0 otherwise

[11] BMD Calculation

= 1 if BMD calculation box is checked
= 0 otherwise

[12] Append or Overwrite Output File

= 1 if Append is selected
= 0 if Overwrite is selected

NOTE: This parameter is automatically set to 0 by the user interface and can only be changed by manually editing the .(d) file!!!!

[13] Smooth Option

= 0 if Unique
= 1 if C-Spline

[14] BMR Type

= 0 if Absolute Dev.
= 1 if Std. Dev.
= 2 if Relative Dev.(Default)
= 3 if Point
= 4 if Extra

[15] BMR (BMR Level)

= User input value (or default of 1.000)

[16] Constant Variance

= 0 if not (the variance is to be modeled as Var(i) = alpha*mean(i)^rho)
= 1 if box is checked (rho is set to 0 in the above equation)

[17] Confidence Level

= User input value (or default of .950)

[18] Alpha Parameter

= User input value if Specified Option is selected
= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[19] Rho Parameter

= 0 if Constant Variance box is checked

If Constant Variance box not checked,

= User input value if Specified Option is selected
= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[20] Control Parameter

= User input value if Specified Option is selected
= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[21] Slope Parameter

= User input value if Specified Option is selected
= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[22] Power Parameter

= User input value if Specified Option is selected
= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[23] Initialize Parameters

= 1 if one or more parameters are set to initialized
= 0 otherwise

[24] Alpha Parameter

= User specified initial value if "initialized" is selected for this parameter
= -9999 if not checked

[25] Rho Parameter

= 0 if Constant Variance box is checked

If Constant Variance box not checked,

= User specified initial value if "initialized" is selected for this parameter
= -9999 if not checked

[26] Control Parameter

= User specified initial value if "initialized" is selected for this parameter
= -9999 if not checked

[27] Slope Parameter

= User specified initial value if "initialized" is selected for this parameter
= -9999 if not checked

[28] Power Parameter

= User specified initial value if "initialized" is selected for this parameter
= -9999 if not checked

[29]-[32] IN THIS ORDER, by checking the column assignment

pull down menus, these fields should contain:

If Group data is entered:

29	30	31	32
Dose name	N name	Mean Name	Std Name

If data is entered:

29	30
Dose name	Response name

etc.

In the same column order as above, this should just be a data listing.

Format Example

[1] Power

[2] BMDS MODEL RUN

[3] Power.SET

[4] Power

[5]	[6]	[7]
1	6	1

[8a]	[8b]	[8c]	[9]	[10]	[11]	[12]	[13]
250	2.22045e-16	1.49012e-8	1	0	1	1	0

[14]	[15]	[16]	[17]
1	1.00	1	0.95

[18]	[19]	[20]	[21]	[22]
-9999	-9999	-9999	-9999	-9999

[23] 0

[24]	[25]	[26]	[27]	[28]
-9999	-9999	-9999	-9999	-9999

[29]	[30]	[31]	[32]
DOSE	NI	MEAN	STD
0	4	38.45	1.1683
8	5	39.56	1.28218
20	4	40.9	1.303
30	4	41.95	1.418203
40	4	42.725	1.438
50	5	43.42	1.45932

Probit and Log-Probit Dichotomous Model Input File Format

[1] Model name, in this case, the string Probit

[2] User notes

[3] Input file name

[4] Output file name

[5] Number of Observations

[6a] Maximum # of iterations

= Default of 250 if user does not input a value
= User input value otherwise

[6b] Rel Function Convergence

= Default of 2.22045e-16 if user does not input a value
= User input value otherwise

[6c] Parameter Convergence

= Default of 1.49012e-8 if user does not input a value

= User input value otherwise

[7] BMDL Curve Calculation

= 1 if BMDL Curve Calculation box is checked
= 0 otherwise

[8] Log transformation

= 1 if Log transformation is to be used
= 0 otherwise

[9] Restrict Slope

= 1 if Restrict Slope >= 1 box is checked
= 0 otherwise

[10] BMD Calculation

= 1 if BMD calculation box is checked
= 0 otherwise

[11] Append or Overwrite Output File

= 1 if Append is selected
= 0 if Overwrite is selected

NOTE: This parameter is automatically set to 0 by the user interface and can only be changed by manually editing the .(d) file!!!!

[12] Smooth Option

= 0 if Unique
= 1 if C-Spline

[13] BMR (BMR level)

= User input value (or default of .100)

[14] Risk Type

= 0 if Extra
= 1 if Added

[15] Confidence Level

= User input value (or default of .950)

[16] Background Parameter

= User input value if Specified Option is selected
= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value or if Log transformation not selected

[17] Slope Parameter

= User input value if Specified Option is selected
= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[18] Intercept Parameter

= User input value if Specified Option is selected
= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[19] Initialize Parameters

= 1 if one or more parameters are set to initialized
= 0 otherwise

[20] Background Parameter

= User specified initial value if "initialized" is selected for this parameter
= -9999 if "initialized" is not selected or if Log transformation not selected

[21] Slope Parameter

= User specified initial value if "initialized" is selected for this parameter
= -9999 if "initialized" is not selected

[22] Intercept Parameter

= User specified initial value if "initialized" is selected for this parameter
= -9999 if "initialized" is not selected

[23] Dose Name

[24] Response Name

[25] Constant String: NEGATIVE_RESPONSE

Data:

Dose in first column
Response in Second
Total minus Response in third column

Example Format

[1] Probit

[2] BMDS MODEL RUN

[3] EXAMPLE.SET

[4] EXAMPLE

[5] 4

[6a]	[6b]	[6c]	[7]	[8]	[9]	[10]	[11]	[12]
250	2.22045e-16	1.49012e-8	1	0	0	1	1	0

[13]	[14]	[15]
0.10	0	0.95

[16]	[17]	[18]
-9999	-9999	-9999

[19] 0

[20]	[21]	[22]
-9999	-9999	-9999

[23]	[24]	[25]
Dose	Resp	NEGATIVE_RESPONSE
0	3	47
50	6	44
100	10	40
150	19	31

Quantal Linear Dichotomous Model Input File Format

[1] Model name, in this case, the string QuantalLinear

[2] User notes

[3] Input file name

[4] Output file name

[5] Number of Observations

[6a] Maximum # of iterations

= Default of 250 if user does not input a value
= User input value otherwise

[6b] Rel Function Convergence

= Default of 2.22045e-16 if user does not input a value
= User input value otherwise

[6c] Parameter Convergence.

= Default of 1.49012e-8 if user does not input a value
= User input value otherwise

[7] BMDL Curve Calculation

= 1 if BMDL Curve Calculation box is checked
= 0 otherwise

[8] This parameter is set to 0 by the user interface, but is ignored when running the Quantal Linear model.

[9] BMD Calculation

= 1 if BMD calculation box is checked
= 0 otherwise

[10] Append or Overwrite Output File

= 1 if Append is selected
= 0 if Overwrite is selected

NOTE: This parameter is automatically set to 0 by the user interface andcan only be changed by manually editing the .(d) file!!!!

[11] Smooth Option

= 0 if Unique
= 1 if C-Spline

[12] BMR (BMR level)

= User input value (or default of .100)

[13] Risk Type

= 0 if Extra
= 1 if Added

[14] Confidence Level

= User input value (or default of .950)

[15] Background Parameter

= User input value if Specified Option is selected
= -9999 if Specified is not selected or when the user selects the Specified option, but does not

enter a value

[16] Slope Parameter

= User input value if Specified Option is selected
= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[17] Power parameter - for the Quantal Linear model, Power is set to a constant value of 1, regardless of what appears here in the input file.

[18] Initialize Parameters

= 1 if one or more parameters are set to initialized
= 0 otherwise

[19] Background Parameter.

= User specified initial value if "initialized" is selected for this parameter
= -9999 if "initialized" is not selected

[20] Slope Parameter

= User specified initial value if "initialized" is selected for this parameter
= -9999 if "initialized" is not selected

[21] Power Parameter - Constant value -9999 for Quantal Linear model.

[22] Dose Name

[23] Response Name

[24] Constant String: NEGATIVE_RESPONSE

Data:

Dose in first column
Response in Second
Total minus Response in third column

Example Format

[1] QuantalLinear

[2] BMDS MODEL RUN

[3] EXAMPLE.SET

[4] EXAMPLE

[5] 4

[6a]	[6b]	[6c]	[7]	[8]	[9]	[10]	[11]
250	2.22045 e-16	1.49012 e-8	1	1	1	1	0

[12]	[13]	[14]
0.10	0	0.95

[15]	[16]	[17]
-9999	-9999	1

[18] 0

[19]	[20]	[21]
-9999	-9999	-9999

[22]	[23]	[24]
Dose	Resp	NEGATIVE_RESPONSE
0	3	47
50	6	44
100	10	40
150	19	31

Rai and Van Ryzin Nested Model Input File Format

[1] Model name, here constant string RaiVR

[2] User notes

[3] Input file name

[4] Output file name

[5] Number of Observations

[5a] Number of Dose groups

[6a] Maximum # of iterations

= Default of 250 if user does not input a value
= User input value otherwise

[6b] Rel Function Convergence

= Default of 2.22045e-16 if user does not input a value
= User input value otherwise

[6c] Parameter Convergence.

= Default of 1.49012e-8 if user does not input a value
= User input value otherwise

[7] BMDL Curve Calculation

= 1 if BMDL Curve Calculation box is checked
= 0 otherwise

[8] Restrict Power >= 1 (Note: Power = Rho parameter in model)

= 1 if Restrict Power >= 1 box is checked
= 0 otherwise

[9] BMD Calculation

= 1 if BMD calculation box is checked
= 0 otherwise

[10] Fixed Size

= 1 if Ctrl Group Mean selected
= 0 if overall mean selected

[11] Append or Overwrite Output File

= 1 if Append is selected
= 0 if Overwrite is selected

NOTE: This parameter is automatically set to 0 by the user interface and can only be changed by manually editing the .(d) file!!!!

[12] Smooth Option

= 0 if Unique
= 1 if C-Spline

[13] BMR (BMR level)

= User input value (or default of .100)

[14] Risk Type

= 0 if Extra
= 1 if Added

[15] Confidence Level

= User input value (or default of .950)

[16] Alpha Parameter

= User input value if Specified Option is selected
= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[17] Rho Parameter

= User input value if Specified Option is selected
= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[18] Beta Parameter

= User input value if Specified Option is selected
= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[19] Theta1 Parameter

= User input value if Specified Option is selected
= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[20] Theta2 Parameter

= User input value if Specified Option is selected
= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[21] Phi1 Parameter

= User input value if Specified Option is selected
= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[22] Phi2 Parameter

= User input value if Specified Option is selected
= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[23] Phi3 Parameter

= User input value if Specified Option is selected
= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[24] Phi4 Parameter

= User input value if Specified Option is selected
= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[24+] Phi5 through Phi10 if necessary (as many Phi parameters as dose groups)

= User input value if Specified Option is selected
= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[25] Initialize Parameters

= 1 if one or more parameters are set to initialized
= 0 otherwise

[26] Alpha Parameter

= User specified initial value if "initialized" is selected for this parameter
= -9999 if not checked

[27] Rho Parameter

= User specified initial value if "initialized" is selected for this parameter
= -9999 if not checked

[28] Beta Parameter

= User specified initial value if "initialized" is selected for this parameter
= -9999 if not checked

[29] Theta1 Parameter

= User specified initial value if "initialized" is selected for this parameter
= -9999 if not checked

[30] Theta2 Parameter

= User specified initial value if "initialized" is selected for this parameter
= -9999 if not checked

[31] Phi1 Parameter

= User specified initial value if "initialized" is selected for this parameter
= -9999 if not checked

[32] Phi2 Parameter

= User specified initial value if "initialized" is selected for this parameter
= -9999 if not checked

[33] Phi3 Parameter

= User specified initial value if "initialized" is selected for this parameter
= -9999 if not checked

[34] Phi4 Parameter

= User specified initial value if "initialized" is selected for this parameter
= -9999 if not checked

[34+] Phi5 through Phi10 if necessary (as many Phi parameters as dose groups)

= User specified initial value if "initialized" is selected for this parameter
= -9999 if not checked

[35] Dose Name

[36] Response Name

[37] Constant String: NEGATIVE_RESPONSE

[38] Litter Size

Data:

Dose in first column
Response in Second
Total (Litter Size) minus Response in third column
Litter Size

Example Format

[1] RaiVR

[2] BMDS MODEL RUN

[3] NCTR31.SET

[4] NCTR31

[5]	[5a]
40	4

[6a]	[6b]	[6c]	[7]	[8]	[9]	[10]	[11]	[12]
250	2.22045e-16	1.49012e-8	1	0	1	1	1	0

[13]	[14]	[15]
0.05	0	0.95

[16]	[17]	[18]	[19]	[20]
-9999	-9999	-9999	-9999	-9999

[21]	[22]	[23]	[24+]
-9999	-9999	-9999	-9999

[25] 0

[26]	[27]	[28]	[29]	[30]
-9999	-9999	-9999	-9999	-9999

[31]	[32]	[33]	[34+]
-9999	-9999	-9999	-9999

[35]	[36]	[37]	[38]
Dose	resp	nega_resp	Liter
0	0	13	13
0	4	10	14
0	1	12	13
0	2	10	12

0	2	10	12
0	2	9	11
0	2	5	7
0	0	12	12
0	2	10	12
0	0	9	9
25	4	9	13
25	4	8	12
25	3	11	14
25	7	3	10
25	5	6	11
25	3	9	12
25	1	11	12
25	5	8	13
25	3	8	11
25	5	11	16
50	3	6	9
50	10	6	16
50	10	3	13
50	3	5	8
50	5	4	9
50	7	4	11
50	5	3	8
50	3	9	12
50	8	3	11
50	6	3	9
100	10	4	14
100	2	1	3
100	13	1	14
100	3	3	6
100	10	1	11
100	9	1	10
100	9	1	10
100	6	3	9
100	5	4	9
100	7	2	9

Weibull Dichotomous Model Input File Format

[1] Model name, in this case, the string Weibull

[2] User notes

[3] Input file name

[4] Output file name

[5] Number of Observations

[6a] Maximum # of iterations

= Default of 250 if user does not input a value
= User input value otherwise

[6b] Rel Function Convergence

= Default of 2.22045e-16 if user does not input a value
= User input value otherwise

[6c] Parameter Convergence.

= Default of 1.49012e-8 if user does not input a value
= User input value otherwise

[7] BMDL Curve Calculation

= 1 if BMDL Curve Calculation box is checked
= 0 otherwise

[8] Restrict power >= 1

= 1 if Restrict Power >= 1 box is checked
= 0 otherwise

[9] BMD Calculation

= 1 if BMD calculation box is checked
= 0 otherwise

[10] Append or Overwrite Output File

= 1 if Append is selected
= 0 if Overwrite is selected

NOTE: This parameter is automatically set to 0 by the user interface and can only be changed by manually editing the .(d) file!!!!

[11] Smooth Option

= 0 if Unique
= 1 if C-Spline

[12] BMR (BMR level)

= User input value (or default of .100)

[13] Risk Type

= 0 if Extra
= 1 if Added

[14] Confidence Level

= User input value (or default of .950)

[15] Background Parameter

= User input value if Specified Option is selected
= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[16] Slope Parameter

= User input value if Specified Option is selected
= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[17] Power parameter

= User input value if Specified Option is selected
= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[18] Initialize Parameters

= 1 if one or more parameters are set to initialized
= 0 otherwise

[19] Background Parameter.

= User specified initial value if "initialized" is selected for this parameter
= -9999 if "initialized" is not selected

[20] Slope Parameter

= User specified initial value if "initialized" is selected for this parameter
= -9999 if "initialized" is not selected

[21] Power Parameter

= user specified initial value if "initialized" is selected for this parameter
= -9999 if "initialized" is not selected

[22] Dose Name

[23] Response Name

[24] Constant String: NEGATIVE_RESPONSE

etc.

Data:

Dose in first column
Response in Second
Total minus Response in third column

Example Format

[1] Weibull

[2] BMDS MODEL RUN

[3] EXAMPLE.SET

[4] EXAMPLE

[5] 4

[6a]	[6b]	[6c]	[7]	[8]	[9]	[10]	[11]
250	2.22045e-16	1.49012e-8	1	1	1	1	0

[12]	[13]	[14]
0.10	0	0.95

[15]	[16]	[17]
-9999	-9999	-9999

[18] 0

[19]	[20]	[21]
-9999	-9999	-9999

[22]	[23]	[24]
Dose	Resp	NEGATIVE_RESPONSE
0	3	47
50	6	44
100	10	40
150	19	31

Exponential Continuous Models Input Format

[1] Model Name, in this case, the constant string Exponential_beta

[2] User Notes

[3] Input file name

[4] Output data file name

[5] Input Type

= 1 if entered as group data (e.g., Dose, N, Mean, Std.)
= 0 if individual animal data (e.g., Dose, Response) are entered

[6] A count of the number of observations
[7] Adverse Direction

= 0 if Automatic (adverse direction with increasing dose estimated by model)
= 1 if Up (dose-response curve trends up with increasing dose)
= -1 if Down (dose-response curve trends down with increasing dose)

OTHER PARAMETERS CONTROLLING WHICH MODELS ARE RUN

[8a] Maximum # of iterations

= Default of 250 if user does not input a value
= User input value otherwise

[8b] Rel Function Convergence

= Default of 2.22045e-16 if user does not input a value
= User input value otherwise

[8c] Parameter Convergence.

= Default of 1.49012e-8 if user does not input a value
= User input value otherwise

[9] BMDL Curve Calculation

= 1 if BMDL Curve Calculation box is checked
= 0 otherwise

[10] BMD Calculation

= 1 if BMD calculation box is checked
= 0 otherwise

[11] Append or Overwrite Output File

= 1 if Append is selected
= 0 if Overwrite is selected

NOTE: This parameter is automatically set to 0 by the user interface and can only be changed by manually editing the .(d) file!!!!

[12] Smooth Option

= 0 if Unique
= 1 if C-Spline

[13] BMR Type

= 0 if Absolute Dev.
= 1 if Std. Dev.
= 2 if Relative Dev.
= 3 if Point
= 4 if Extra

[14] BMRF (BMR Level)

= User input value (or default of 1.000)

[15] Constant Variance

= 0 if not (the variance is to be modeled as Var(i) = alpha*mean(i)^rho)
= 1 if box is checked (rho is set to 0 in the above equation)

[16] Confidence Level

= User input value (or default of .950)

[17] Alpha Parameter

= User input value if Specified Option is selected
= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[18] Rho Parameter

= 0 if Constant Variance box is checked
If Constant Variance box not checked,
= User input value if Specified Option is selected
= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[19] a Parameter

= User input value if Specified Option is selected
= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[20] b Parameter

= User input value if Specified Option is selected
= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[21] c Parameter

= User input value if Specified Option is selected
= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[22] d Parameter

= User input value if Specified Option is selected
= -9999 if Specified is not selected or when the user selects the Specified option, but does not enter a value

[23] Initialize Parameters

= 1 if one or more parameters are set to initialized
= 0 otherwise

[24] Alpha Parameter

= User specified initial value if "initialized" is selected for this parameter
= -9999 if not checked

[25] Rho Parameter

= 0 if Constant Variance box is checked
If Constant Variance box not checked,
= User specified initial value if "initialized" is selected for this parameter
= -9999 if not checked

[26] a Parameter

= User specified initial value if "initialized" is selected for this parameter
= -9999 if not checked

[27] b Parameter

= User specified initial value if "initialized" is selected for this parameter
= -9999 if not checked

[28] c Parameter

= User specified initial value if "initialized" is selected for this parameter
= -9999 if not checked

[29] d Parameter

= User specified initial value if "initialized" is selected for this parameter
= -9999 if not checked

Note: In the Exponential Beta software, no initial values may be specified by the user. Leave all these entries as is (with "-9999").

[30]-[33] IN THIS ORDER, by checking the column assignment pull down menus, these fields should contain:
If Group data are entered:

[29]	[30]	[31]	[32]
Dose name	N name	Mean Name	Std Name

If data are entered:

[29]	[30]
Dose name	Response name

[etc.]
In the same column order as above, this should just be a data listing.

Format Example
[1] PROAST
[2] BMDS MODEL RUN
[3] Exponential.dax
[4] Exponential

[5]	[6]	[7]

1 6 1

[8a]	[8b]	[8c]	[9]	[10]	[11]	[12]
250	2.22045e-16	1.49012e-8	0	1	1	0

[13]	[14]	[15]	[16]
1	1.00	1	0.95

[17]	[18]	[19]	[20]	[21]	[22]
-9999	-9999	-9999	-9999	-9999	-9999

[23] 0

[24]	[25]	[26]	[27]	[28]	[29]
-9999	-9999	-9999	-9999	-9999	-9999

[30]	[31]	[32]	[33]
DOSE	NI	MEAN	STD
[etc.]			
0	4	38.45	1.1683
8	5	39.56	1.28218
20	4	40.9	1.303
30	4	41.95	1.418203
40	4	42.725	1.438
50	5	43.42	1.45932